Synthetic Approaches to Skeletally Diverse Sultams Using Vinyl- and α-Halo Benzenesulfonamides

By

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Abstract

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The development of new chemical methods to generate novel and diverse structures to probe chemical space is an important aspect of early phase drug discovery. Diversity-Oriented Synthesis (DOS) is a powerful strategy that seeks to generate chemical methods capable of delivering an array of molecular scaffolds with structural and functional diversity. Ultimately, these methods can be adapted to produce molecular libraries. It is the purpose of this thesis to highlight a series of new chemical methods that deliver an array of drug-like sultam scaffolds to be screened for broad biological activity in the molecular library program run by the National Institutes of Health.

The first project described in chapter one of this dissertation includes the synthesis of a collection of diverse bi- and tricyclic sultams in an overall DOS approach utilizing a ring-opening metathesis / ring-closing metathesis / cross metathesis (ROM–RCM–CM) cascade strategy. A variety of functionalized, tricyclic sultams were generated as precursors derived from a diastereoselective IMDA reaction in good yields and selectivity. The ROM–RCM–CM strategy to produce skeletal and appendage-based diverse sultams is presented.

The second project is the generation of diverse sultams utilizing *α,β*-

unsaturated γ- and δ-sultams. These 5- and 6-membered sultams were prepared and applied to further diversifications using aza-Michael reactions, cycloadditions, alkylation/benzylations and propargylation-[3+2]-cycloadditions. Utilizing the aza-Michael reaction, we have developed an efficient protocol for the synthesis of a 141-member library collection of isothiazolidine 1,1-dioxide derivatives.

The last project outlined in chapter four is the synthesis of novel 7- and 8-membered tricyclic, biaryl sultams using an intramolecular Pd-catalyzed *C*-arylation reaction. Namely, in the amino ester-derived sultams, remote 1,5- and 1,6-asymmetric induction emanating from the external stereogenic center is operative, whereby a favorable Cα–H/S=O *syn* pentane interaction, is the source of asymmetric induction for a highly atropdiastereoselective thermodynamic equilibration process yielding a low energy conformer of "like" configuration (S,S_a).

In the course of X-ray crystallographic analysis, as well as detailed NMR studies, we uncovered a number of notable and interesting structural features of the 7-membered amino ester-derived sultams in both solid and solution phases that confirm a structure as a single conformer (>95:5) containing biaryl axial chirality of "like" configuration (S,S_a) with respect to the stereogenic center in the external side chain. Moreover, variable temperature NMR analysis has indicated that the axis of chirality at the biaryl bond has a relatively small interconversion barrier that allows for this rapid thermodynamic equilibration of the "like" and "unlike" atropdiastereomers. Detailed variable NMR analyses on a number of analogs, *vide infra*, point to rotamer dynamics (about the N–C bond in the external side chain) and

ring size of the corresponding benzothiazepine (n = 1)/benzothiazocine (n = 2) 1,1-dioxides as governing factors in this notable thermodynamic equilibration of atropdiastereomers. Current efforts are focused on the computational calculation for the energy barrier between two atropdiastereomers interconversion, as well as the further development of an "atropdiastereoselective" *C*-arylation process. In addition, future studies will continue to probe the dynamic factors involved in the origins of atropselectivity. Utilizing this methodology, we are also generating additional libraries of diverse tricyclic, biaryl sultams for high throughput screening of biological activity with our collaborators at the National Institutes of Health.

To Mom and Dad, my sisters and brother

For all support and love

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Synthetic Approaches to Skeletally Diverse Sultams

Using Vinyl- and α-Halo Benzenesulfonamides

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Abbreviations

Å	angstrom
Al_2O_3	aluminum oxide
Ar	aryl
aq	aqueous
BCl_3	boron trichloride
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
^{i}Bu	*iso*-butyl
^{n}BuLi	*n*-butyllithium
^{t}BuOH	*tert*-butanol
Bu_4NOAc	tetrabutylammonium acetate
$CDCl_3$	chloroform (deuterated)
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CM	cross metathesis
$CpRuCl(PPh)_3$	chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium
Cs_2CO_3	cesium carbonate
CuI	copper(I) iodide
Cy	cyclohexyl

$CuSO_4•5H_2O$	copper(II) sulfate pentahydrate
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	diemethyl sulfoxide (deuterated)
DOS	diversity-oriented synthesis
Et	ethyl
Et_2AlCl	diethylaluminum chloride
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtO_2CCHO	ethyl glyoxylate
EtOH	ethanol
eq	equivalent(s)
EVE	ethyl vinyl ether
FGP	functional-group-pairing
h	hour(s)

HCl	hydrochloric acid
HF-py	hydrogen fluoride pyridine
H_2O	water
HIV	human immunodeficiency virus
HRMS	high resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	hertz
I_2	iodine
IMDA	intramolecular Diels–Alder
IR	infrared spectrometry
K_2CO_3	potassium carbonate
KHMDS	potassium bis(trimethylsilyl)amide
KOAc	potassium acetate
KOH	potassium hydroxide
LHMDS	lithium bis(trimethylsilyl)amide
$LiAlH_4$	lithium aluminum hydride
LiOH	lithium hydroxide
M	moles per liter
Me	methyl
MeOH	methanol
MeOH-d_4	methanol (deuterated)
Me_3SI	trimethylsulfonium iodide

$MgSO_4$	magnesium sulfate
mmol	millimole(s)
μm	micromiter
mL	milliliter(s)
μL	microliter(s)
Mp	melting point
MVK	methyl vinyl ketone
*m*W	microwave
$NaBH_4$	sodium borohydride
NaH	sodium hydride
NaN_3	sodium azide
$NaNO_2$	sodium nitrite
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
$PdCl_2(PPh)_3$	bis(triphenylphosphine)palladium(II) dichloride
$Pd(OAc)_2$	palladium(II) acetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl

PMB	*p*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
^{i}Pr	*iso*-propyl
RCEM	ring-closing enyne metathesis
RCM	ring-closing metathesis
RO	ring-opening
ROESY	rotating frame nuclear Overhauser effect spectroscopy
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
rt	room temperature
SM	starting material
S_N2	substitution nucleophilic bimolecular
SPE	solid phase extraction
TBSCl	*tert*-butyldimethylsilyl chloride
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	tandem metathesis
Tr	trityl (triphenylmethyl)
*p*TsOH•H_2O	*p*-toluenesulfonic acid monohydrate

Chapter 1

Introduction: Biologically Active Sultams

1.1 Introduction

Sultams (cyclic sulfonamides) represent a class of non-natural amide surrogates that have emerged as viable medicinal chemotypes due to their wide chemical and biological profiles.[1] Historically, sultams have found widespread use with utility ranging from chiral auxiliaries in asymmetric synthesis,[2,3] artificial sweeteners (saccharin) in the food industry,[4] and ionic liquids serving as novel reaction media,[5] to a growing number of medicinal agents. To date, there are several sultam-containing drugs for use in the treatment of a variety of disease states, including acquired immune deficiency syndrome (AIDS), diabetes, arthritis, hepatitis C virus (HCV), respiratory syncytial virus (RSV) and human leukocyte elastase (HLE) to name a few. The rapid rise of sultams in drug discovery and development, beacons the call for a review covering their impressive biological activities. In this regard, it is the goal of this introductory chapter to highlight recent investigations on biologically active compounds containing the sultam moiety. After a brief introductory paragraph on the unique properties of sulfonamides that affect the syntheses of their cyclic counterparts, the chapter will be organized according to the nature of the biologically active, heterocyclic sultam motif.

1.1.1 Properties of Sulfonamides

The aforementioned biological activity of sultams has prompted several efforts towards their synthesis. In 2011, Majumdar and coworker published an extensive work in *ACS Chemical Reviews* that highlights recent developments of

synthetic methods to access condensed (fused) sultams, including ring-closing metathesis (RCM), Diels-Alder, and [3+2]-cycloaddition reactions.[6] In addition this body of work, our group has recently reported a number of methodologies for generation of various sultams.[7]

Although some methodologies for sultam synthesis are comparable to those of lactam synthesis, there is significant difference embedded in the physical properties of sulfonamides, when compared to their amide counterparts, that open reaction pathways to sulfonamides that are unavailable to amides. Among several parameters, the presence of two electronegative oxygen atoms within the SO_2 moiety impart greater inductive effect within sulfonamide **1.1** than amide **1.2**. Computational calculations show a more electron deficient sulfur atom within the SO_2 than the carbon atom of the lactam.[8] Furthermore, this trend affects the electrophilic behavior at the β-carbon of vinyl sulfonamides when compared to the β-carbon of vinyl amides. Ultimately, this imparts prominent Michel accepting ability for vinyl sulfonamides that have been exploited in our laboratories.[7a,b,7g-i] In particular, intramolecular oxa-Michael reactions of vinyl sulfonamides occur smoothly to obtain 7- and 8-membered sultams, the later in a unique "contra Baldwin Rules", 8-*endo*-trig pathway that is most likely aided by additional differences of atomic radius between sulfur and carbon (sulfur 100 pm, carbon 70 pm).

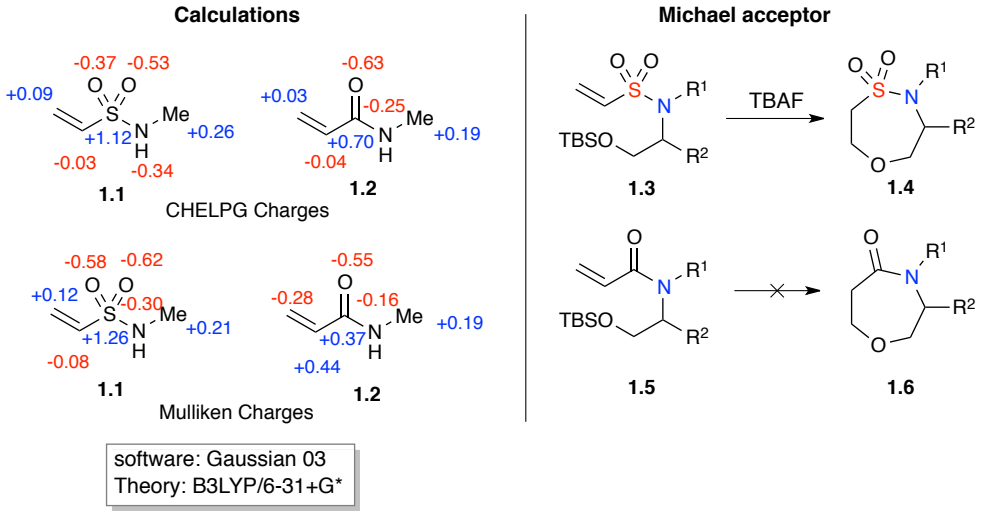


Figure 1.1

The enhanced electron deficiency of SO_2 over the C=O group also affects general *pKa* properties, which for benzenesulfonamides and benzamides, are 16.1 and 23.3 (in DMSO), respectively.[9] This enhanced acidity enables mild alkylation conditions for secondary benzenesulfonamides such as **1.7** (Cs_2CO_3, RX, rt) when compared to benzamides **1.9**, which require strong bases and thermal conditions to produce tertiary benzamides (Figure 1.2). Moreover, fluoro-substituted benzenesulfonamides undergo facile nucleophilic aromatic substitution (S_NAr) reactions under mild reaction conditions (**1.11** to **1.12**), while the corresponding benzamides (**1.13**) fail to undergo S_NAr reactions even under forcing conditions. This enhanced behavior has been exploited by Fukuyama and coworkers, who, in 2004, reported an innovative approach for secondary amine synthesis using the *pKa* properties nitrobenzenesulfonamides.[10] This method has been widely utilized in both industry and academia.

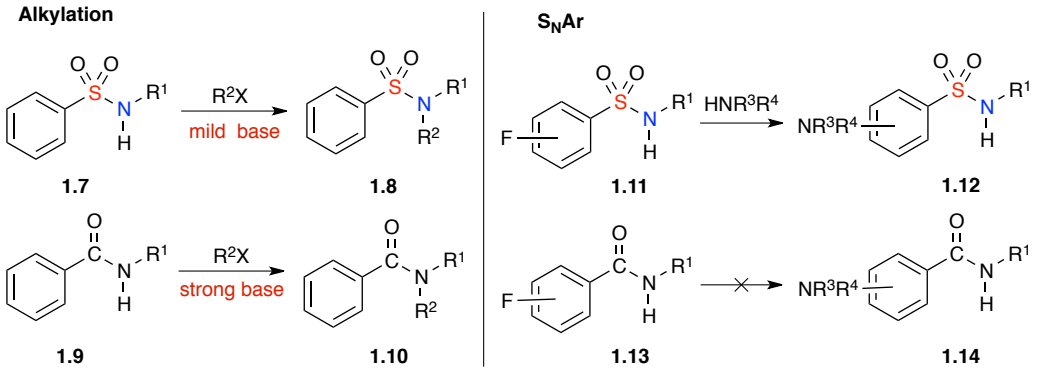


Figure 1.2

Additionally, sulfamide derivatives can undergo ring-closing metathesis (RCM) to provide the corresponding cyclic sulfamide compounds.[11] However, RCM of the corresponding urea analogues did not produce any cyclized products. The origins of this discrepancy are detailed in Matthew McReynolds thesis.[12]

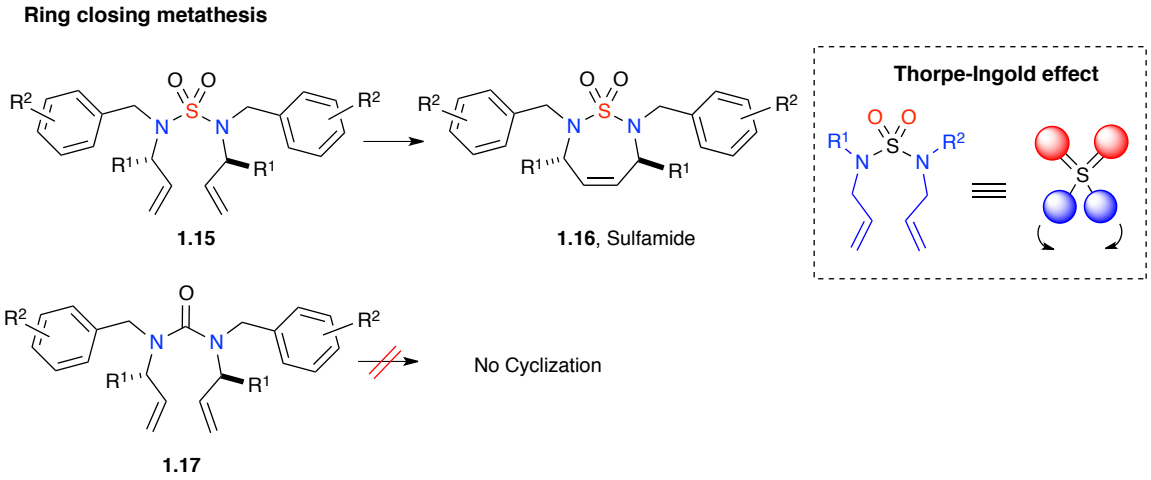
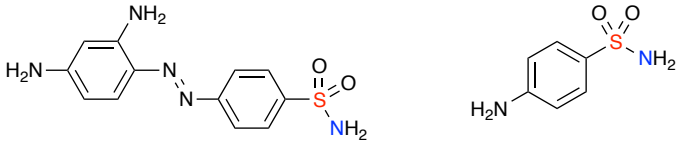


Figure 1.3

1.1.2 Sultam Bioactivities

In the early 1900's, sulfonamide chemistry advanced at a rapid pace, due to widespread use in azo dyes, which were highly employed in the production of fibers and textiles. Efforts to improve dye properties, found that introduction of a sulfonamide group (-SO_2NH-) generated dyes with superior stability to light, greater water solubility during application, and greater fixation to fibers.[13]

In 1932, the investigation about the action of various dyes in streptococcal infections in mice was conducted by the research group of Bayer laboratory in Germany. The red dye called prontosil (**1.18**) exhibited antibacterial properties,[14] and three years later it was discovered that prontosil is metabolized to active sulfanilamide (**1.19**) in the body (Figure 1.4). This important discovery led to its clinical use for the treatment of bacterial infections. In addition, sulfonamides have shown several interesting biological activities including, inhibition of carbonic anhydrase (acetazolamide),[15] anticancer activity (agent E7070)[16] and antibacterial activity (sulfathiazole).[17]



Prontosil (**1.18**) Sulfanilamide (**1.19**)

Figure 1.4

Ensuing chemical studies involving p*Ka* measurements also revealed that this versatile entity is comparable to the carboxyl group and therefore, it has been utilized as a carboxyl isostere. Moreover, sulfonamides are non-hydrolyzable amide

surrogates and several studies have shown the utility of sulfonamides as ideal functional groups in the synthesis of peptidomimetics.[18] In 1999, Liskamp and coworkers reported that replacement of an amide by a sulfonamide in peptides provided more stability towards protease-catalyzed degradation.[19] Based on this observation, they have been used as transition-state analogues for amide bond hydrolysis and have been found applications as potential HIV protease inhibitors.[18c] Furthermore, sulfonamides now represent an important class of drugs with several types of pharmacological agents having antibacterial, antitumor, anti-carbonic anhydrase, diuretic, hypoglycemic, anti-thyroid, or protease inhibitory activity.[20]

Similar to sulfonamides, the bioactivities of sultams bear resemblance to lactams. However, in addition to the aforementioned differences between sulfonamides and amides, the presence of an extra H-bond acceptor within the SO_2 moiety, a more acidic sulfonamide N–H, and the geometric layout of SO_2, may provide supplementary benefits for sultams to interact with proteins. In this regard, sultams have surfaced as a non-natural class of biologically active compounds with a wide array of activities. In this chapter, we will give a brief historical account of FDA approved sultam-containing drugs and then provide a preliminary review of the literature pertaining to bioactivity, with organization focusing on 5-, 6- and 7-membered sultams.

1.2 Sultam-Containing Drugs

The rich history of antibacterial sulfonamides, *vide supra*, laid the foundation for the development of acetazolamide (**1.20**) in 1950[21] as a carbonic anhydrase inhibitor that is used to treat glaucoma and seizures.[22] Brinzolamide [trade name: Azopt (**1.21**)] is also a carbonic anhydrase inhibitor and is introduced for the treatment of glaucoma.[23] Further investigations to improve diuretic activity led to the seridenpidous discovery of a number of ring-closed, benzene disulfonamide derivatives (Figure 1.5). These unexpected, cyclized, benzothiadiazine products exhibited enhanced diuretic activity.

In 1957, Chlorothiazide [trade name: Diuril (**1.22**)] was introduced as a thiazide diuretic by Novello and coworkers from Merck Sharp and Dohme Research laboratories.[24] Two years later, benzthiazide [trade name: Exna (**1.23**)] was also synthesized by McLamore and coworkers from Pfizer laboratory and used for high blood pressure as well as edema.[25] However, benzthiazide **(1.23)** is no longer available in the United States. In Switzerland, it is still available in combination with the potassium-sparing diuretic triamterene. Bendroflumethiazide [trade name: Naturetin (**1.24**)] was synthesized in 1959[26] and is used for treatment of hypertension as well as heart failure. Methyclothiazide [trade name: Aquatensen, Enduron (**1.25**)] was developed by Vernsten and coworkers in 1960, and is used to treat high blood pressure and fluid retention.[27] Hydrochlorothiazide [trade name: HydroDiuril, Esidrix (**1.26**)] has been used for the treatment of hypertension for more than 50

years.[28] Trichlormethiazide [trade name: Achletin (**1.27**)] has similar properties to hydrichlorothiazide. Polythiazide [trade name: Aquatensen, Renese (**1.28**)] are used

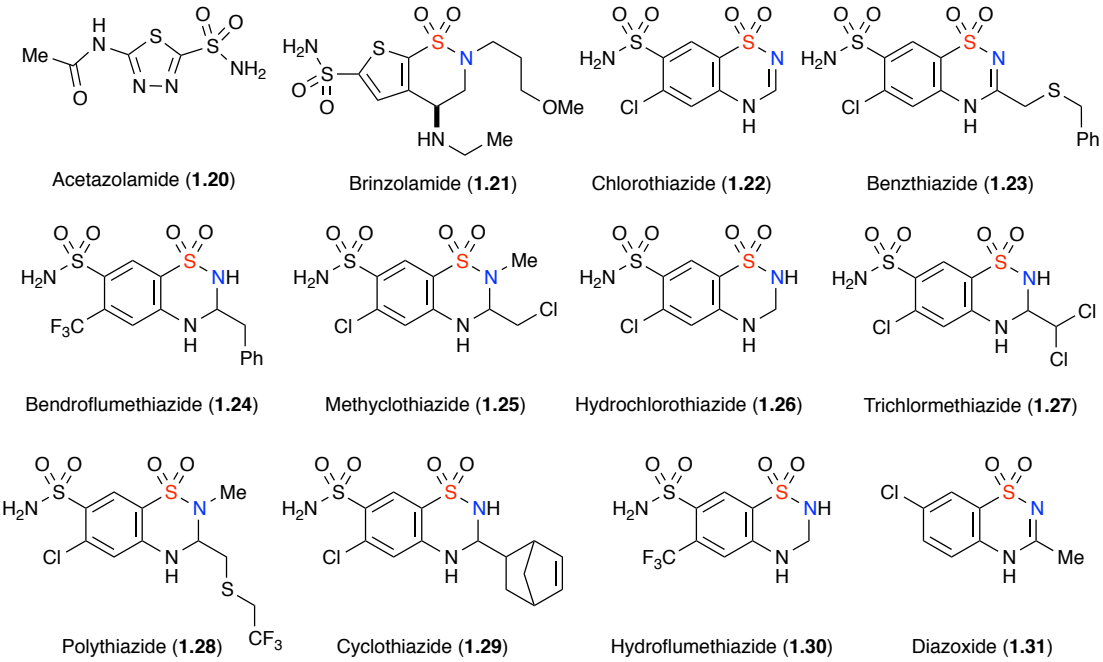


Figure 1.5

in the treatment of hypertension, congestive heart failure, edema, diabetes insipidus, renal tubular acidosis, and the prevention of kidney stones.[29] Cyclothiazide [trade name: Anhydron (**1.29**)] was introduced in the United States in 1963 by Eli Lilly and in 1993, it was discovered as a positive allosteric modulator of AMPA receptor.[30] Ten years later, cyclothiazide was also found acting as a $GABA_A$ receptor negative allosteric modulator.[31] Cyclothiazide is used as adjunctive therapy in edema and is also used for treatment of hypertension. Hydroflumethiazide [trade name: Saluron, Diucardin (**1.30**)] is a drug for acute or chronic vascular hypertension.[32] Diazoxide [trade name: Proglycem (**1.31**)] is potassium channel activator and inhibits the secretion of insulin from the pancreas.[33]

A second family of sultam drugs is a class of medications called non-steroidal anti-inflammatory drugs (NSAIDs), including piroxicam [trade name: Feldene (**1.32**)],[34] meloxicam [trade name: Mobic (**1.33**)][35] lornoxicam [trade name: Xefo (**1.34**)][36] and tenoxicam [trade name: Mobiflex (**1.35**)][37] (Figure 1.6). These medicines work *via* non-selective inhibition of cyclooxygenase (COX) imparting both analgesic and antipyretic properties.

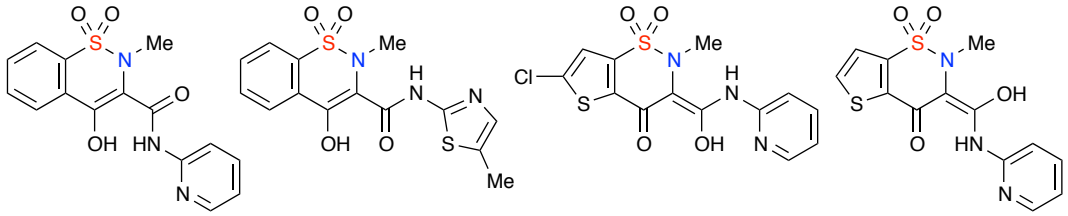


Figure 1.6

Piroxicam (**1.32**) was synthesized by Lombardino and coworkers from Pfizer Laboratory in early 1970[34] and is available in the United Kingdom, Spain, Portugal, Australia, Italy, Brazil and the United States and is manufactured by Pfizer. Meloxicam (**1.33**) was introduced by Boehringer-Ingelheim and inhibits selectively COX-2 over COX-1.[35] Meloxicam (**1.33**) is usually used for pain relief and is available in many countries including the Middle East, Europe, Paraguay, Australia, Canada and Latin America. Lornoxicam (**1.34**)[36] and tenoxicam (**1.35**)[37] are used for the treatment of various types of pain resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica, and other inflammations. In particular, tenoxicam (**1.35**) is available in the United Kingdom and is manufactured by Roche.

1.3 Bioactive Compounds containing 5-Membered Sultam Moiety

1.3.1 Naphthoisothiazole 1,1-Dioxide Derivatives

In 2008, Pérez-Pérez and coworkers discovered the first acyclic thymine-base derivatives as a *Mycobacterium tuberculosis* thymidine monophosphate kinase (TMPKmt) inhibitor.[38] Based on the lead compound **1.36**, analogues that differ on thymine base, the spacer that connects the thymine base, the distal 1,8-naphthalimide, and the 1,8-naphthalimide have been synthesized and examined (Figure 1.7). Several compounds in the naphthalimide derivatives show K_i values in the low μM range. Furthermore, a naphtholactam or naphthosultam (compounds **1.37**, **1.38**, and **1.39**) instead of the naphthalimide ring showed K_i values in the submicromolar range.

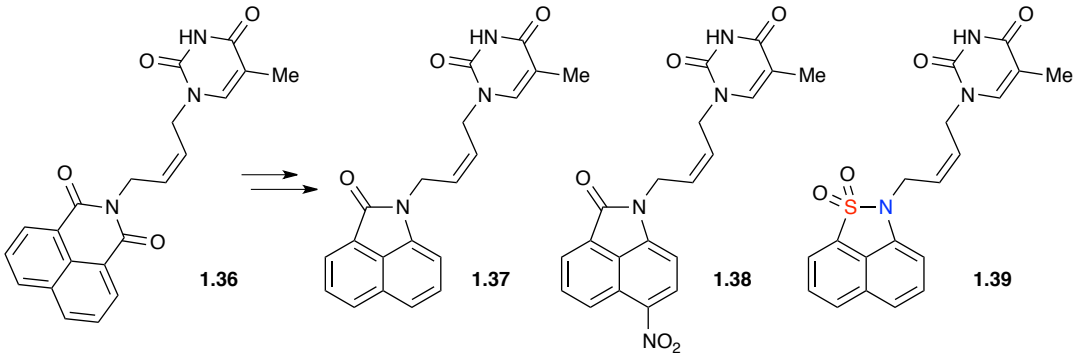


Figure 1.7

In 2012, Kamal and coworkers reported a series of benzo[*c*,*d*]indol-2(1*H*)one-pyrrolobenzodiazepine (PBD) conjugates as potential anticancer agents.[39] The DNA binding ability of these compounds was examined by thermal denaturation studies. Among them, sultam **1.40** exhibited significant DNA binding ability compared to its lactam and alkene analogues. Compound **1.40** displayed better anti-cancer activity against lung cancer cell lines. Additionally, the authors found that cell cycle arrest in

SubG1 phase was observed upon treatment of A549 cells with 1 and 2 μM (IC_{50}) concentrations of compound **1.40**.

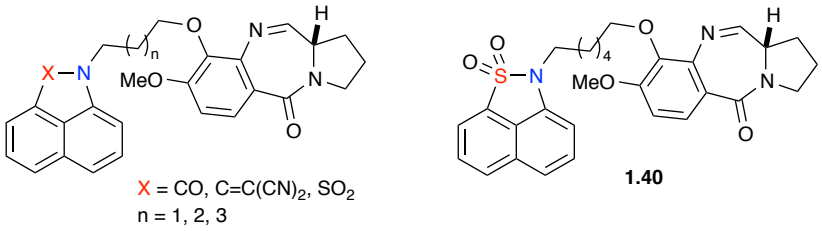


Figure 1.8

2-(Aminoalkyl)naphth[1,8-*cd*]isothiazole 1,1-dioxide derivatives were synthesized by Malleron and coworkers in 1991 as a serotonin subtype (5-HT_2) receptor.[40] All compounds were tested *in vitro* for their binding affinity to rat 5-HT_2, α^1 and D_2 receptors. Most compounds of this series exhibited high affinity for the 5-HT_2 receptor, with good selectivity. In particular, compound **1.41** (RP 62203) revealed high 5-HT_2-receptor affinity (K_i = 0.26 nM) (Figure 1.9).

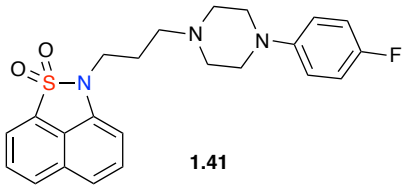


Figure 1.9

1.3.2 1,2-Benzisothiazol-3-one 1,1-Dioxide (Saccharin) Derivatives

1,2-Benzisothiazol-3-one 1,1-dioxide (saccharin) was discovered by Remsen and Fahlberg in 1879.[41] Saccharin with sodium salt is about 500 times sweeter than sugar, therefore has been used as a no calorie sweetener and food additive[42] in the 1970's, but was later banned as a food additive when preliminary studies reported that high doses caused urinary bladder carcinoma in mice.[43] Later saccharin has been found as an important molecular component in a variety of classes of $5HT_{1A}$ antagonists,[44] human leukocyte elastase (HLE) inhibitors,[45] analgetics,[46] human mast cell tryptase inhibitors, [47] and aldehyde dehydrogenase inhibitors. [48] *N*-Alkylarylpiperazine of benzo[*d*]isothiazole [49] and a series of heterocyclic isothiazoles ring were also synthesized and found to display anti-mycobacterium and central nervous system activity.[50,51]

In 2011, a series of *N*-basic side chains was derived from 2,3-dihydro-2*H*-3-oxobenzo[*d*]isothiazole and aliphatic or aromatic aldehydes by Hamama and coworkers (Figure 1.10).[52] Compounds **1.42**, **1.43c** and **1.44** revealed remarkable anti-microbial activity, and compounds **1.43a**, **1.43b**, **1.45a**, **1.45b** and **1.46** displayed high anti-oxidant activity. These compounds also appeared to impart a high degree of DNA protection from the damage induced by Bleomycin.

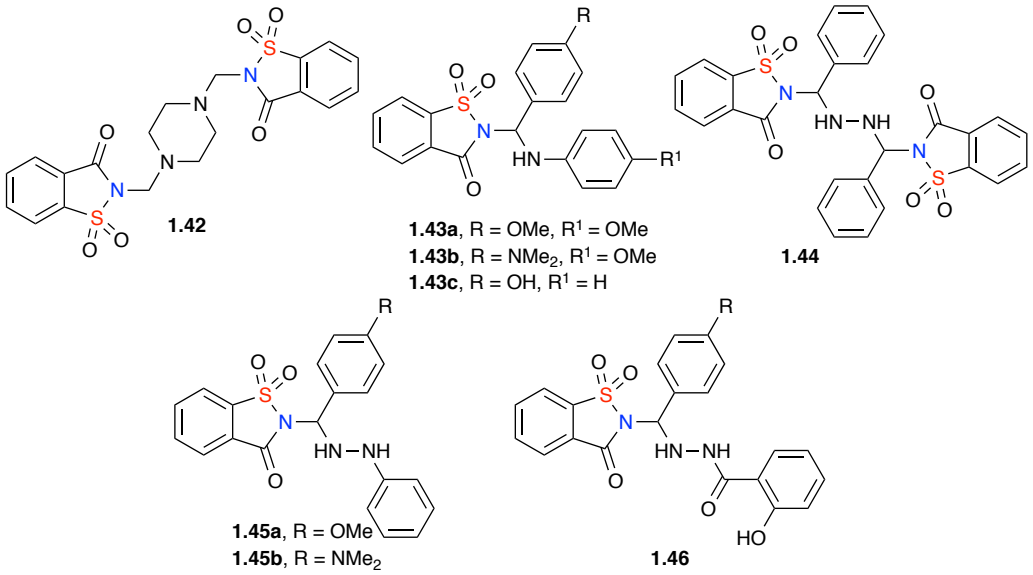


Figure 1.10

Saccharin derivatives have been widely used as human leukocyte elastase (HLE) inhibitors.[45] Mechanistic studies suggest elastase inhibition involving an S_N2' displacement step in which Ser-195 of the enzyme attacks the carbonyl group of saccharin and with subsequent departure of the sulfonamide leaving group (Figure 1.11). In this regard, the Groutas group discovered that the activities of compounds **1.47**–**1.49** were related to their leaving group ability in the system.[53] In 1995, Desai and coworkers synthesized saccharin derivatives including alkyl and aryl phosphonates and phosphinates as an acid-based leaving group.[54] Compound **1.50**, a diethyl phosphonate derivative, exhibited high *in vivo* activity.

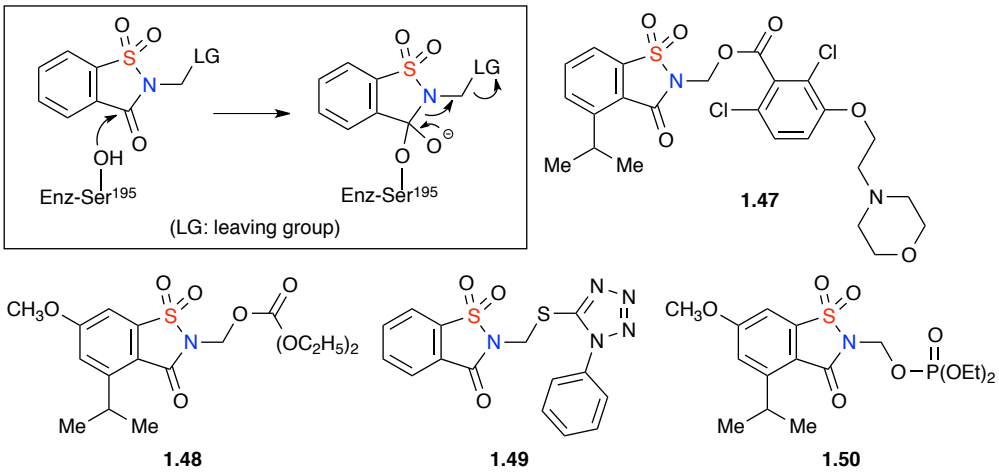


Figure 1.11

In 2006, Otto *et al*. prepared pseudosaccharinamine derivatives as potential elastase inhibitors (Figure 1.12).[55] Several pseudosaccharinamine derivatives were found to be reversible inhibitors of porcine pancreatic elastase (PPE) and HLE. Diversification of the most potent compounds, **1.51** and **1.52**, should lead to improve activities of HLE inhibitors.

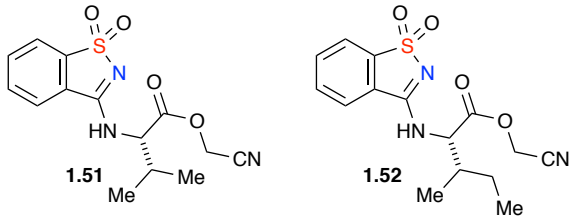


Figure 1.12

In 2006, Güzel and coworkers synthesized a series of saccharin derivatives containing dithiocarbamate and dithiocarbonate side chains. Dithiocarbamates and dithiocarbonates have been reported to possess a variety of biological activities including fungicidal, antibacterial and anticancer effects.[56] Saccharin was treated with potassium dithiocarbamates and potassium dithiocarbonates to provide various

N,*N*-disubstituted dithiocarbamate and *O*-alkyldithiocarbonate saccharin derivatives (**1.53** and **1.54** in Figure 1.13).[57] Several compounds of the derivatives exhibited *in vitro* anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv and anti-tumor activity.

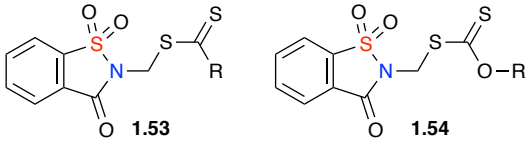


Figure 1.13

In 2011, Zwanenburg and coworker prepared a series of strigolactone (SL) analogues derived from phthalimide, saccharin, *p*-tolylmalondialdehyde, benzoic and salicylic acid.[58] These SL derivatives are highly active as germination stimulants of seeds of *Striga hermonthica* and *Orobanche cernua*. The authors also observed that the compound from a direct coupling of saccharin with the chlorobutenolide exhibited a high germination activity towards *O. cernua* seeds. The compound **1.55** was a very active germinating agent (Figure1.13), prompting belief that these SL mimics appear to be new types of potential germination stimulants.

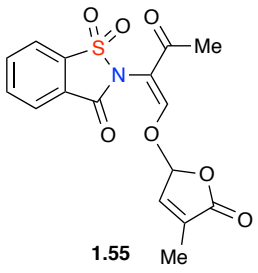
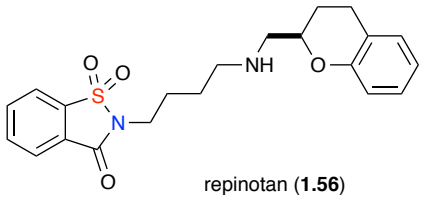


Figure 1.14

Repinotan (BAYx3702, **1.56**) is a high-affinity 5-HT_{1A} receptor agonist (Figure 1.15).[59] Repinotan (**1.56**) was synthesized as a potential treatment for

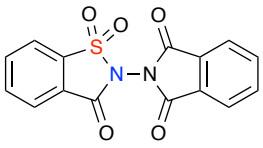
ischemic stroke and traumatic brain injury and was trialed up to phase II, however, it did not go further in clinical trials because of insufficient efficacy of repinotan.[60]



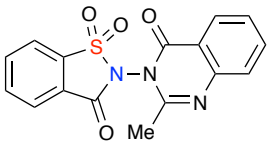
repinotan (**1.56**)

Figure 1.15

In 2010, Zakharova and coworkers prepared *N*,*N*'-linked benzo-annulated isothiazol-3(2*H*)-one 1,1-dioxide analogues as inhibitors toward human leukocyte elastase (HLE) and acetylcholinesterase (AChE).[61] Two compounds, **1.52a** and **1.52b** were found to be inhibitors of HLE and AChE (Figure 1.16). The derivatives were also examined as potential precursors of nitrogen-centered radicals using 266 nm laser flash photolysis.



1.57



1.58

Figure 1.16

In 2002, benzenesulfonamide derivatives containing the pyrazole and oxadiazole moieties were synthesized by El-Sanbbagh and coworkers.[62] These derivatives are structurally similar to the COX-2 inhibitor celecoxib (Celebrex®). A pharmacological study of the pyrazole analogues showed that several compounds exhibited higher analgesic and anti-inflammatory activities than celecoxib, specifically the acyclic sulfonamide **1.59** and sultam **1.60** (Figure 1.17). Some of the

derivatives containing pyrazole revealed potent analgesic activities and significant anti-inflammatory activities.

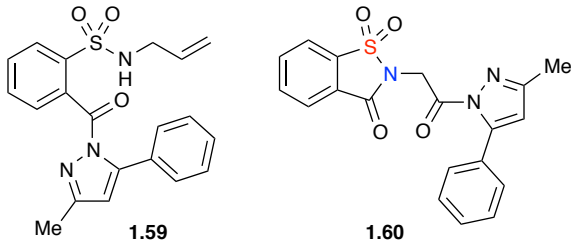
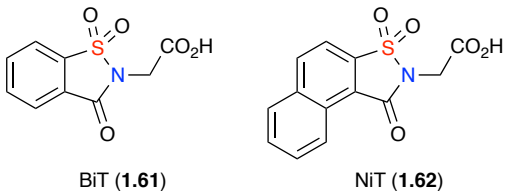


Figure 1.17

In 2005, La Motta and coworkers introduced a series of 1,1-dioxide-benzo[*d*]isothiazol-3-one alkanoic acid (BiT, **1.61**) derivatives as aldose reductase (ALR2) inhibitors.[63] These compounds appeared to be relatively potent inhibitors, with IC_{50} values in the μM range. Among them, the 4-NO_2 acetic acid derivative showed the highest activity (IC_{50} = 5.5 μM). It is known that the *in vitro* ALR2 inhibitory effectiveness of a compound is a function both of its acidic group ionized at the anion-binding site and of its lipophilic part interacting with the enzyme hydrophobic catalytic site, which terminate the inhibitory potency and the selectivity of an inhibitor. Therefore, increasing the overall lipophilicity of BiT (**1.61**) inhibitors may improve the *in vitro* activity and, possibly, in ALR2 selectivity (Figure 1.18). Based on this rationale, La Motta and coworkers decided to introduce a benzoisothiazole backbone generating the acetic acid derivatives of 3,3-dioxide-1,2-dihydronaphtho[1,2-*d*]-isothiazol-1-one (NiT, **1.62**) as better ALR2 inhibitors.



BiT (**1.61**) NiT (**1.62**)

Figure 1.18

1.3.3 Benzo[*d*]isothiazole 1,1-Dioxide Derivatives

In 2006, Evans and coworkers from GlaxoSmithKline Pharmaceuticals synthesized benzothiadiazine analogues **1.63** as potential HCV polymerase inhibitors (Figure 1.19).[64] Two years later, Zhou and coworkers from Anadys laboratories reported a related series of pyridazinone-containing NS5B inhibitors (**1.64**), which also interact to the same region of the enzyme.[65]

In 2008, Kim and coworkers from Anadys laboratories synthesized a series of benzo[*d*]isothiazole-1,1-dioxides, which essentially introduced the 1,1-dioxoisothiazole fragment instead of the benzothiazine moiety of compound **1.64**.[66] Among them, compound **1.65** displayed the most potent activities against the genotype 1b HCV polymerase (IC_{50} < 10 nM) and against a genotype 1b replicon (EC_{50} = 70 nM) in cell culture. However, DMPK properties results for selected compounds revealed that the incorporation of polar substituents on the C4 position was important for enhancing the biological potencies of these molecules and their oral pharmacokinetic (PK) properties. Although compounds **1.63** and **1.64** derivatives were potent inhibitors of HCV polymerase both in enzymatic and replicon assays, they revealed low oral bioavailability and high clearance because of metabolic instability of the benzothiazine ring.

In 2009, Vicente and coworkers prepared a series of inhibitors of HCV polymerase. The authors reported sultam **1.66** as the most potent analogue in their HCV replicon assay with moderate pharmacokinetic properties.[67] However, it turned out that the reduced potency in the presence of 40% human serum limited the development of this compound as a drug candidate.

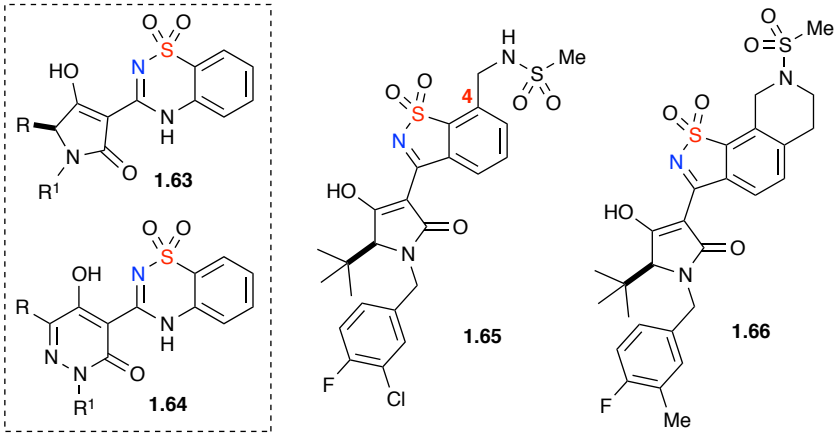
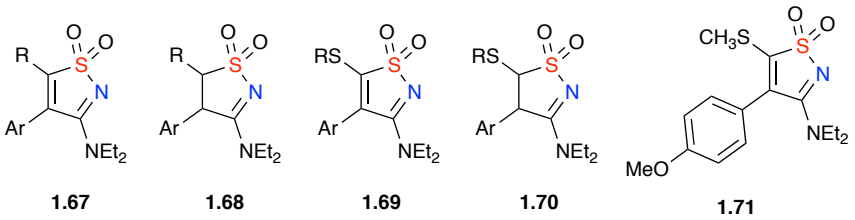


Figure 1.19

1.3.4 Isothiazole 1,1-Dioxide Derivatives

In 2002, Clerici and coworkers synthesized a series of isothiazole dioxides and tested them as inhibitors of *Trypanosoma brucei* protein farnesyltransferase (PFTase) from the parasite that causes African sleeping sickness.[68,69] Among these derivatives (**1.67**–**1.70**), compound **1.71** exhibited the most potent activity against protein farnesyltransferase and smooth muscle cell (SMC) proliferation by interfering with the G0/G1 phase of the cell cycle (Figure 1.20).

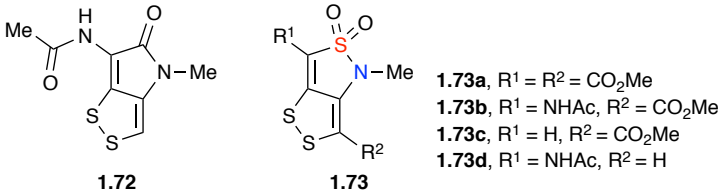


1.67 **1.68** **1.69** **1.70** **1.71**

Figure 1.20

1.3.5 2,3-Dihydroisothiazole 1,1-Dioxide Derivatives

Based on the commercially available antibiotic thiolutin (**1.72**), an agent that suppresses tumor-induced angiogenesis, the sulfonyl analogues (so called "sulfothiolutin", **1.73**) were prepared by Stachel and coworkers in 2005 (Figure 1.21).[70] The sultams **1.73a**, **1.73b**, **1.73c**, and **1.73d** displayed anti-mycobacterial activities comparable to their lactam analogues from the preliminary test.

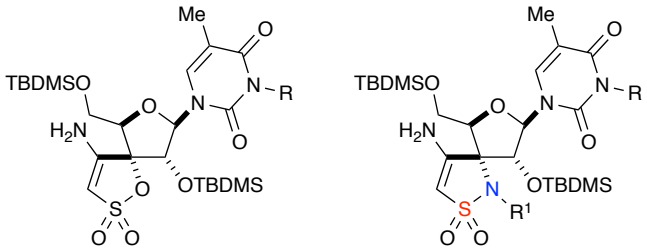


1.72 **1.73**

Figure 1.21

[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide)thymine (TSAO-T) derivatives were synthesized as a specific anti-HIV agent by Postel and coworkers in 2005.[71] As one of the SAR studies, the cyclic sulfonate fragment of compound **1.74** was replaced with a sultam to produce a family of aza analogues of TSAO (ATSAO, **1.75**). Some of compounds displayed HIV-1 specific reverse transcriptase inhibitory activities. Furthermore, ATSAO-Boc^{3}T with the unsubstituted isothiazolic ring was found to be

only 2- to 7-fold less active against HIV-1 replication in MT-4 and CEM cells than TSAO-T (Figure 1.22).



1.74
TSAO-T, R = H
TSAO-m^3T, R = CH_3

1.75
ATSAO-T derivatives
R = H, Boc, CH_3
R^1 = H, CH_3

Figure 1.22

1.4 Bioactive Compounds Containing 6-Membered Sultam Moiety

1.4.1 1,2-Thiazinane 1,1-Dioxide Derivatives

In 2004, sultam hydroxamates have been introduced as a new template for matrix metalloproteinase (MMP) inhibition by Cherney and coworkers.[72] Compound **1.76** displayed the most active inhibitor (MMP-2 IC_{50} =1 nM) with excellent selectivity over MMP-1 and with good oral bioavailability (F = 43%) in mouse (Figure 1.23). Based on the X-ray crystal structure of **1.76** in MMP-13, the authors demonstrated that the hydrogen bonds (between the pro-(*S*) sultam sulfonyl and the Leu-185) and major side binding in the active site (S1 pocket of the MMPs) are essential. The authors also examined these sultam analogues for potent TNF-α converting enzyme (TACE) inhibitors.[73] They studied on structural differences between the MMP and TACE S1 pockets and the known advantageous fit of a 2-

methyl-4-quinolinylmethoxyphenyl group into this region. Based on these studies, compound **1.77** was identified as a potent TACE inhibitor (IC_{50} = 3.7 nM) that lacked MMP-1, -2, -9, and -13 activity.

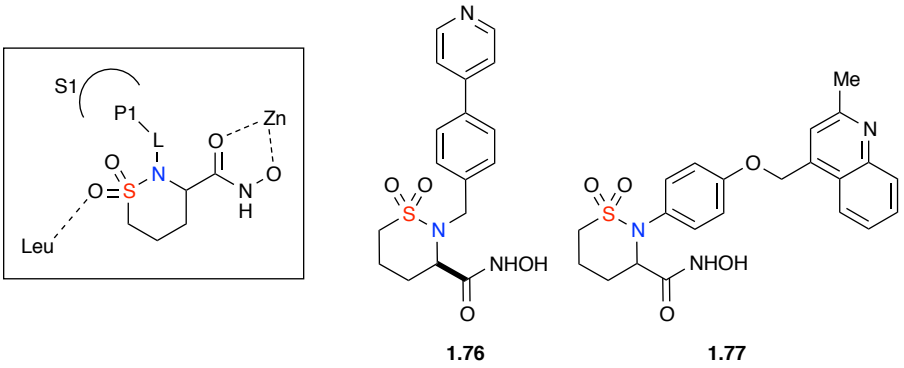


Figure 1.23

1.4.2 Benzodithiazine 1,1-Dioxide Derivatives

Saczewski and coworker reported cyclic analogues of 2-mercaptobenzenesulfonamides **1.78** and **1.79** that possessed anti-HIV and anticancer properties (Figure 1.24). Based on these biological activities the authors extended their work to explore a new series of 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine derivatives with heteroaryloxycarbonyl or heteroarylcarbamoyl substituents at position 7 as potential antitumor agents.[74] All synthesized compounds were tested at the National Cancer Institute (NCI) for their activities against a panel of 60 tumor cell lines. Compounds **1.80**, **1.81** and **1.82** displayed the most potent of all derivatives tested. Compound **1.80** exhibited activities against lung cancer cell lines and compound **1.82** was shown to be a selective inhibitor for leukemia cell lines.

In 2003, Saczewski research group also synthesized a series 4-dimethylaminopyridinium (6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)methanides and examined them for *in vitro* antitumor activities.[75] Among the aminium salts, 4-dimethylaminopyridinium 4-chlorobenzoyl cyano (6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)methanide (**1.83**) exhibited significant activity (log GI_{50} and log TGI < –8.00) and high selectivity for the lung HOP-92 and melanoma UACC-257 cell lines. Furthermore, the authors noticed that the benzodithiazines containing carbon atom at the C3 position displayed antitumor and/or anti-HIV activities. Therefore, they performed further investigations for a series of benzodithiazines fragments bearing a carbon atom at position 3.[76] Compound **1.84** displayed potent activities (GI_{50} = 6.9–49.4 μM) against 49 tumor cell lines, and also exhibited a selective high activity against leukemia CCRF-CEM cell line.

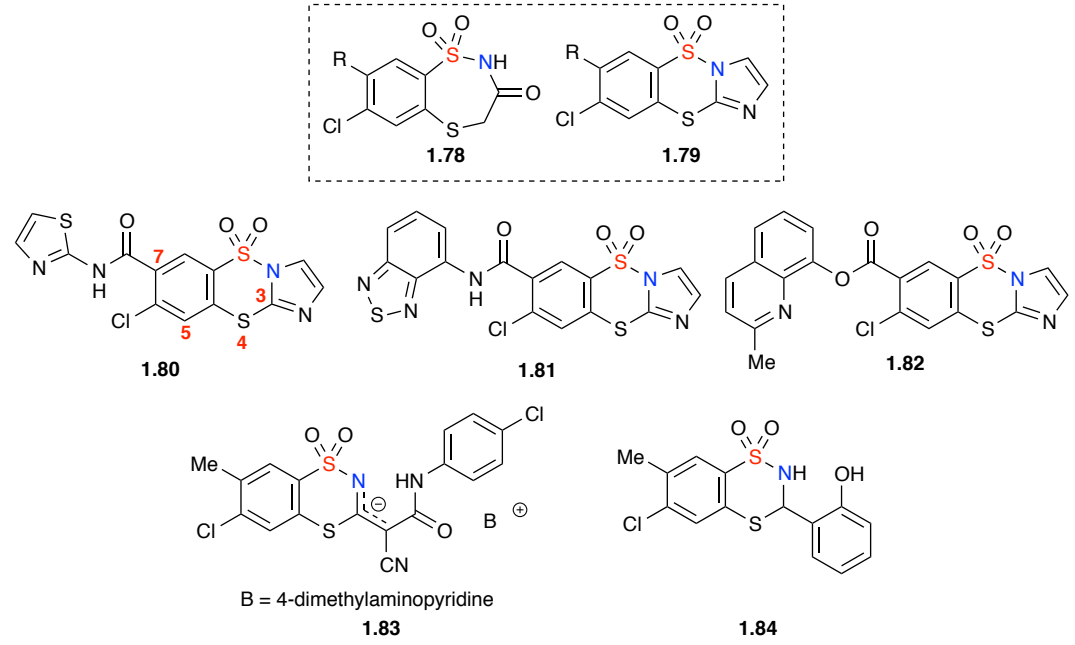


Figure 1.24

Previously, Saczewski *et al.* reported dithiazine-carboxylic acid derivatives with remarkable anti-cancer activity. Because these type of compounds displayed several biological activities, they also synthesized 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine 5,5-dioxide derivatives as potential antitumor or anti-HIV agents.[77] The *in vitro* antitumor and anti-HIV-1 activities of the compounds were examined across a panel of cell lines. The benzodithiazine-dioxide **1.86** exhibited low μM activity in several cell lines including leukemia, lung, melanoma, ovarian, and renal cancer cells (GI_{50} = 1–2 μM) (Figure 1.25). Furthermore, benzodithiazine-dioxide **1.87** also showed anti-HIV-1 activity (EC_{50} = 0.94 μM) without any significant cytotoxicity at 200.0 μM. These investigations indicated that the substitution of the methyl group at the 7-position by a nitrile is crucial for affecting selectivity.

The previous studies with *N*-(azolyl or azinyl)-2-mercaptobenzenesulfonamides (MBSAs type I, **1.85**) showed promising anticancer activities and potent HIV-1 integrase inhibition. In 2003, Pomarnacka and coworker noticed that cyclic sulfonamide derivatives of 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine of type II, **1.79** displayed anti-cancer properties (Figure 1.25).[78] The authors designed a novel tricyclic ring system as a lead structure to improve anti-cancer activity. Among them, compounds **1.88** and **1.89** were the most potent. In 2006, Pomarnacka's research group also designed compounds bearing electron-withdrawing substituents at both positions 2 and 7. Two series of 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-arylsemicarbazides and 2-arylamino-8-

chloro-5,5-dioxo[1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines were synthesized and tested for their *in vitro* cytotoxic potency against 12 human cancer cell lines.[79] Compounds **1.90a** and **1.90b** were the most potent among examined derivatives and displayed inhibitory activity against cancer cell lines generally better than cisplatin. The authors observed that compounds containing electron-withdrawing substituents at both positions 2 and 7 of the triazolobenzodithiazine scaffold exhibited activity.

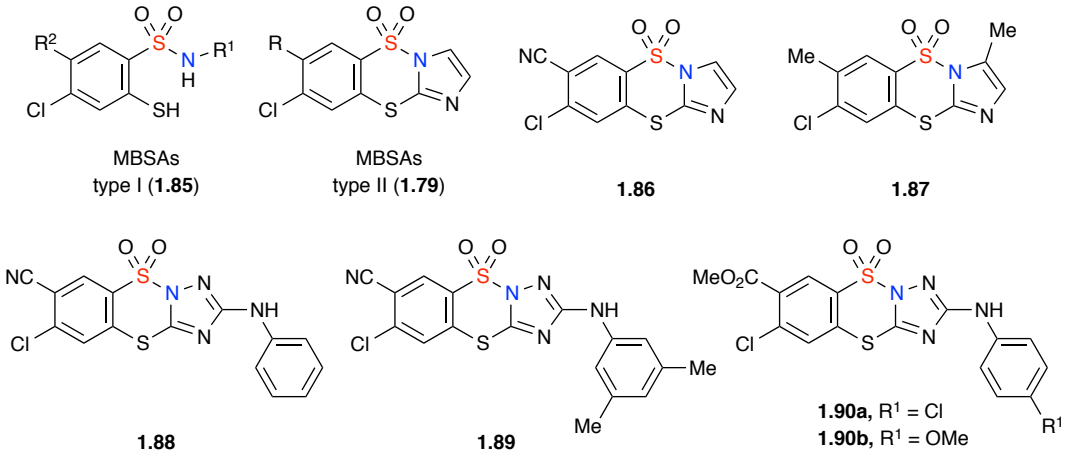
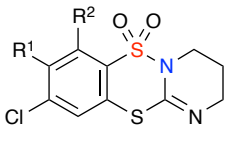


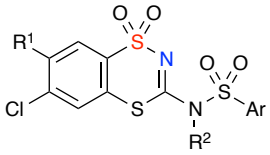
Figure 1.25

In 2006, Saczewski *et al.* reported a series of benzodithiazines-dioxide derivatives with both antiviral and anticancer activities. In order to obtain compounds with significant antiviral properties, they replaced the imidazole rings with pyrimidine rings (Figure 1.26).[80] The authors successfully determined a lead compound with representative anti-HIV-1 activity (EC_{50} = 0.09 μM) in cell-based assays by NCI. The most active compounds were 4-chloro-2,3,4-trihydropyrimido[1,2-*b*][1,4,2]benzodithiazines **1.91a**, **1.91b**, and **1.91c** (EC_{50} = 0.09–4.75 μM). In particular, pyrimido[1,2-*b*][1,4,2]benzodithiazine **1.91c**, which

bears an electron-donating methyl group at position 7 displayed the most potent anti-HIV activity (EC_{50} = 0.09 μM).

In 2007, Saczewski and coworkers also synthesized a series of *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)arylsulfonamides as potential anticancer agents.[81] Several sultam compounds depending on their structure displayed high (GI_{50} = 0.03–5.0 μM) activities against most of the tumor cell lines. In particular, compounds **1.92a**, **1.92b**, **1.92c**, and **1.92d** were the most potent among them (Figure 1.26). Compound **1.92d**, with a 5-Br-thienyl group at the Ar position, showed remarkably improved potency against melanoma UACC-257 cell line; and thus may serve as a lead compound for selective antineoplastic agents.





1.91a, R^1 = H, R^2 = H
1.91b, R^1 = Me, R^2 = H
1.91c, R^1 = H, R^2 = Me

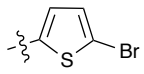
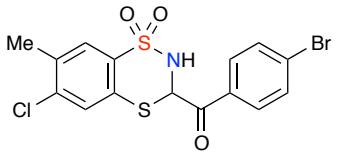
1.92a, R^1 = Me, R^2 = 4-ClPh, Ar = Ph
1.92b, R^1 = EtOCO, R^2 = Ph, Ar = 4-O_2NPh
1.92c, R^1 = NC, R^2 = Ph, Ar = 4-ClPh
1.92d, R^1 = NC, R^2 = Ph, Ar = 

Figure 1.26

In 2009, Saczewski *et al.* synthesized 3-aroyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazine derivatives as potential HIV-1 integrase (IN) inhibitors.[82] Several of the generated compounds showed inhibitions of IN-mediated strand transfer reaction, with IC_{50} values ranging from 3 to 30 μM. The 3-(4-bromobenzoyl)-6-chloro-7-methyl-2,3-dihydro-1,1-dioxo-1,4,2-benzodithiazine **1.93** was the most potent (Figure 1.27).

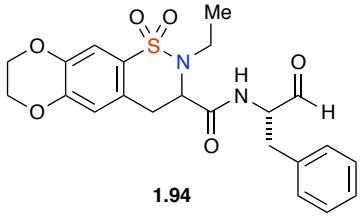


1.93

Figure 1.27

1.4.3 Benzothiazine 1,1-Dioxide Derivatives

In 2001, a series of peptide mimetic aldehyde inhibitors of calpain I was produced by Bihovsky and coworkers.[83] The effect of 2, 6, and 7-benzothiazine substituents and the amino acid was also tested against human recombinant calpain I. Compound **1.94** is a selective inhibitor of calpain I versus cathepsin B probably due to rigidity of the compound **1.94** (Figure 1.28).

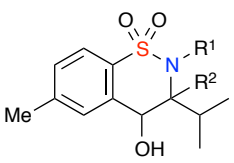


1.94

Figure 1.28

In 2002, 6-methyl-3-isopropyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxides derivatives were derived from *L*-valine as anti-inflammatory agents by Bouraoui and coworkers.[84] Compounds **1.95a–f** were active anti-inflammatory agents in carrageenan-induced rat paw oedema assay in albino rats, and effects of the derivatives were comparable to that of piroxicam as a reference drug (Figure 1.29). The nature of the substituents on the sulfonamide nitrogen and those on C3-position

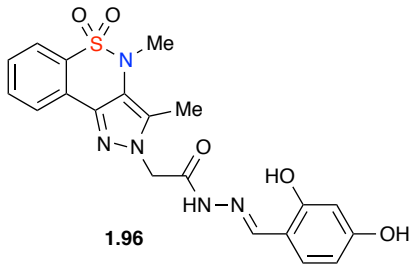
revealed a significant effect on the anti-inflammatory activity. Studies of structure–activity relationships led to a lead compound 2,6-dimethyl-3-isopropyl-1,2-benzothiazin-3,4-diol 1,1-dioxide **1.89f**, which displayed the most potent activity.



1.95a, R^1 = H, R^2 = H
1.95b, R^1 = Me, R^2 = H
1.95c, R^1 = Me R^2 =OH
1.95d, R^1 = H, R^2 = H
1.95e, R^1 = Me, R^2 = H
1.95f, R^1 = Me, R^2 = OH

Figure 1.29

In 2010, Siddiqui *et al.* synthesized *N*'-arylmethylidene-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetohydrazides derivatives starting from saccharine as potential anti-oxidant and anti-bacterial agents. A dihydroxy derivative **1.96** showed the most potent activities against *B. subtillis* and *Escherichia coli* (MIC = 5.0 μg ml^{-1}, Figure 1.30).[85] The lone pairs on oxygen atoms of hydroxyl and methoxy groups of compound **1.96** probably attributed to the activity. Furthermore, compounds containing heteroatoms (nitrogen and sulfur) on the aromatic moiety displayed moderate to high activities against all the bacterial strains.

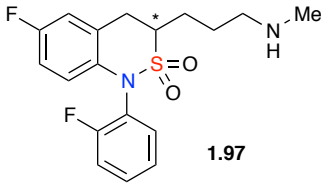


1.96

Figure 1.30

In 2010, Goldberg and coworkers reported two related series of selective norepinephrine reuptake inhibitors based on 3,4-dihydro-1*H*-2,1,3-benzothiadiazine

2,2-dioxide or 3,4-dihydrosulfostyril cores, and evaluated them for monoamine reuptake inhibition.[86] The authors identified that the series' *in vitro* potency and selectivity versus serotonin or dopamine transporter inhibition, and analogues based on both cores were found to be potent and selective norepinephrine reuptake inhibitors (NRIs) from structure–activity relationships. Compound **1.97** was further optimized for both potency and stability, and displayed efficacy in an *in vivo* model of thermoregulatory dysfunction (Figure 1.31).



1.97

Figure 1.31

1.4.4 Benzothiadiazine 1,1-Dioxide Derivatives

In 1993, Pirotte and coworkers synthesized a series of pyrido[4,3-*e*]-1,2,4-thiadiazine 1,l-dioxide derivatives involving different aminoalkyl side chains in the 3-position.[87] The pyridine ring was introduced as a bioisostere of a benzene ring containing an electron-withdrawing substituent (halogeno, nitro, cyano). The three best compounds, **1.98a**, **1.98b** and **1.99**, which showed a maximal inhibition of insulin release at 50 μM, were also investigated at the same concentration for their vasorelaxant activity on K^+-depolarized rat aorta (Figure 1.32).

In 2000, Vega and coworkers noticed that several compounds belonging to the 1,2,6- and 2,1,3-thiadiazine ring systems did not match with the diazoxide pattern in

different pharmacological assays during an investigation focused on the discovery of novel potassium channel openers.[88] These results led them to synthesize new compounds as potassium channel openers in which the benzene ring of known benzothiadiazines was substituted by thiophene (Figure 1.32). From *in vivo* studies, compounds **1.100a**, **1.100b** and **1.100c** were selected for further investigations as antihypertensive agents.

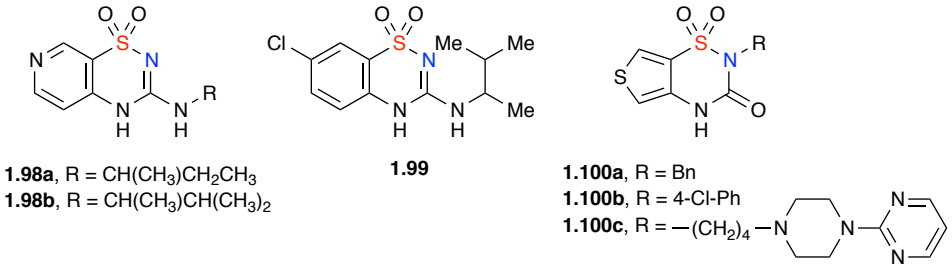
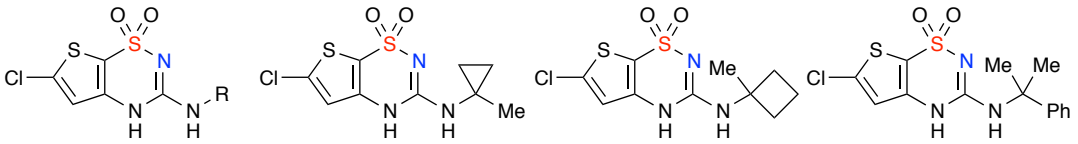


Figure 1.32

Two years later, Hansen *et al.* prepared 6-chloro-3-alkylamino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide derivatives as activators of adenosine 5'-triphosphate (ATP) sensitive potassium (K_{ATP}) channels in the β-cells by measuring effects on membrane potential and insulin release *in vitro*.[89] The authors observed that 6-chloro-3-(1-methylcyclobutyl)amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1.103**) binds as well as activates the SUR1/Kir6.2 K_{ATP} channels in the low nM range and was at least 1000 times more potent than the reference compound diazoxide with respect to inhibition of insulin release from rat islets (Figure 1.33). The compounds 3-propylamino- (**1.101a**), 3-isopropylamino- (**1.101b**), 3-(*S*)-*sec*-butylamino- (**1.101c**), and 3-(1-methylcyclopropyl)amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1.102**) showed inhibitions of insulin secretion in rats with

minimal effects on blood pressure and exhibited good oral pharmacokinetic properties.

In 2006, Hansen and coworkers observed that compound **1.102** (NN414) was a potent opener of Kir6.2/SUR1 K_{ATP} channels, inhibited insulin release *in vitro* and *in vivo*, and preserved beta cell function in preclinical animal models suggesting that such a compound could find use in treatment or prevention of type 1 and type 2 diabetes (Figure 1.33).[90] Compound 6-chloro-3-(1-methyl-1-phenylethyl)amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1.104**), were potent openers of Kir6.2/SUR1 K_{ATP} channels and were suppressed glucose-stimulated insulin release from rat islets *in vitro* (EC_{50} = 0.04 ± 0.01 μM) and *in vivo* (ED_{50} = 4.0 mg/kg) after intravenous or parenteral administration to hyperinsulinemic obese Zucker rats. Structural diversifications of this series of analogues provided compounds with promising pharmacokinetic properties, indicating that brief periods of beta cell rest can be achieved.



1.101a, R = $(CH_2)_2CH_3$
1.101b, R = $CH(CH_3)_2$
1.101c, R = (*S*)-$CH(CH_3)CH_2CH_3$

1.102 (NN414) **1.103** **1.104**

Figure 1.33

Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are a major subdivision of the glutamate receptor family that mediates excitatory synaptic transmission in the brain. One of those modulators is the benzothiadiazide IDRA-21

(**1.105**) which has been reported to enhance synaptic transmission and be effective in behavioral tests, but typically requires threshold concentrations of at least 100 μM to be active *in vitro* (Figure 1.34).[91] In 2002, Chamberlin and coworkers reported the synthesis a series of 5'-alkyl-benzothiadiazide derivatives with IDRA-21 (**1.105**) as lead compound of AMPA receptor modulator and examined them for their potency in modulating AMPA receptor kinetics (Figure 1.34).[92] A significant increase in drug affinity was obtained by alkyl substitution at the 5'-position of IDRA-21. The 5'-ethyl derivative exhibited an EC_{50} value in the order of 22 μM, which was about 30-fold better in affinity than that of IDRA-21. Based on these biological testing results, the authors assumed that the constrained structure of **1.107a** and **1.107b** might be similar to the binding conformation of **1.106a**.

In 2007, Francotte and coworkers synthesized and evaluated biological activities of a series of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides analogues as a positive allosteric modular of the AMPA receptors. The authors observed that analogue **1.108a** containing a fluorine and an ethyl group at C7 and N4 positions exhibited better biological activity among them (Figure 1.34).[93]

In 2010, Francott and coworkers extended their investigations in order to improve biological activity and they observed that compounds **1.108b** and **1.108c** showed a remarkable dose dependent activity after oral administration.[94]

In 2011, Cannazza and coworkers performed more detailed investigations about compound **1.107b** bearing two stereogenic centers (Figure 1.34).[95] The authors prepared all stereoisomers of compound **1.107b**, however, single stereoisomers of

1.107b underwent epimerization of the C3 position in saline solution. Therefore, the epimeric mixtures of **1.107b** were used for biological testing for positive AMPA receptor modulators and the epimeric mixture (3*,6*S*)-**1.107b** was more active than the epimeric mixture (3*,6*R*)-**1.107b**.

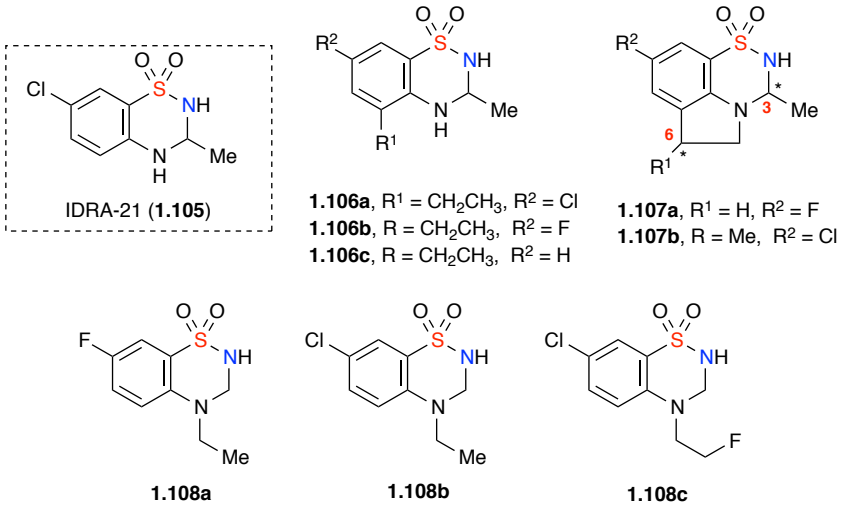
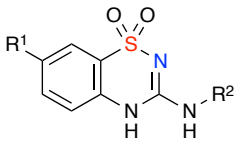


Figure 1.34

In 2003, Pirotte *et al*. synthesized a series of 3-(alkylamino)-7-halo-4*H*-1,2,4-benzothiadiazine 1,1-dioxides as potential tissue-selective pancreatic β-cells K_{ATP} channel openers.[96] From structure-activity relationship studies, introductions of a fluorine atom in the 7-position, and a short linear or cyclic hydrocarbon chain on the nitrogen atom in the 3-position were improved both potency and selectivity for the pancreatic tissue. In addition, strong myorelaxant activity was obtained by introducing a chlorine atom in the 7-position, and a bulky branched alkylamino chain in the 3-position. Compound 3-(ethylamino)-7-fluoro-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**1.109a**) displayed a remarkable inhibitory activity on pancreatic β-cells (IC_{50} = 1 μM) associated with a weak vasorelaxant effect (ED_{50} > 300 μM), whereas 7-

chloro-3-(1,1-dimethylpropyl)amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**1.109b**) was very potent on vascular smooth muscle cells (ED_{50} = 0.29 μM) (Figure 1.35).

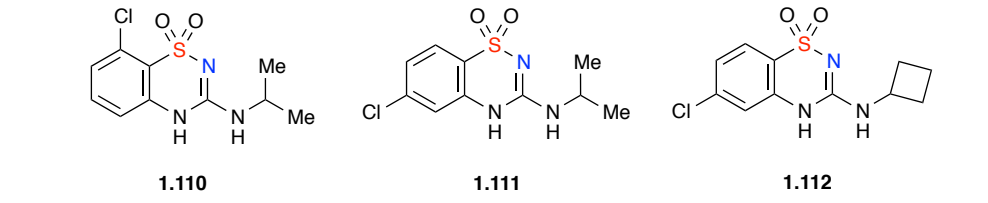


1.109a, R^1 = F, R^2 = CH_3
1.109b, R^1 = Cl, R^2 = $C(CH_3)_2CH_2CH_3$

Figure 1.35

In 2010, Pirotte and coworkers synthesized 5-chloro-, 6-chloro-, and 8-chloro-substituted 3-alkylamino/cycloalkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides to understand biological activity depending on the position of the substituent. Of these derivatives, compounds **1.110**, **1.111**, and **1.112** showed improvement of biological activities and were further identified as K_{ATP} channel openers by radioisotopic measurements conducted on insulin-secreting cells (Figure 1.36).[97] Pirotte and coworkers also explored their work to synthesize 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides diversely substituted in the 7-position.[98] These compounds are structurally related to the previously reported 7-chloro-3-alkylamino/cycloalkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives as potassium channel openers. The natures of the substituent introduced in the 7-position, and the alkylamino side chain in the 3-position were essential for both potency and tissue selectivity of 4*H*-1,2,4-benzothiadiazine 1,1-dioxides. Compounds containing in the 7-position a methyl or a methoxy group or devoid of a substituent in this position and bearing an ethyl, an isopropyl, or a cyclobutylamino group in the 3-position exhibited more potent and selective inhibitors of insulin

release from rat pancreatic *β*-cells (**1.113a**,**b**, **1.113e**,**f**, and **1.114d**). Compounds 3-alkylamino-7-trifluoromethyl- (**1.114a**–**c**),[98] compounds, 3-alkylamino-7-pentyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**1.113c**, **d**) showed a significant myorelaxant activity on the rat aorta ring. In particular, the 3-alkylamino-7-pentyl derivative **1.111c** showed a notable selectivity for the vascular smooth muscle tissue.



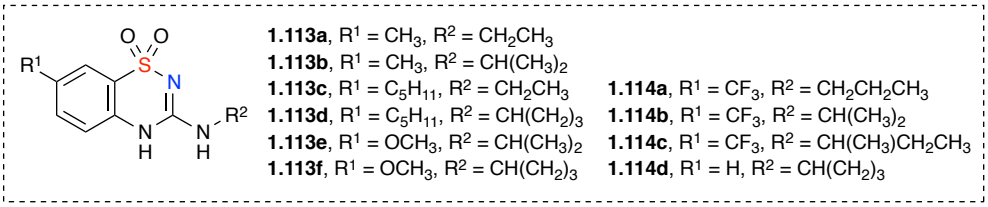


Figure 1.36

In 2005, Tait and coworkers synthesized a series of 1,2,4-benzothiadiazine derivatives with an arylpiperazine moiety linked at position 3 of the heterocyclic ring as α_1-adrenoceptor subtypes (α_{1A}, α_{1B} and α_{1D}) and human cloned 5-HT_{1A} receptor ligands.[99] Compound **1.115** was determined as a novel α_{1D} antagonist with high selectivity over the 5-HT_{1A} receptor (Figure 1.37). Compound **1.116** also displayed better affinity as well as selectivity for the 5-HT_{1A} receptor.[99]

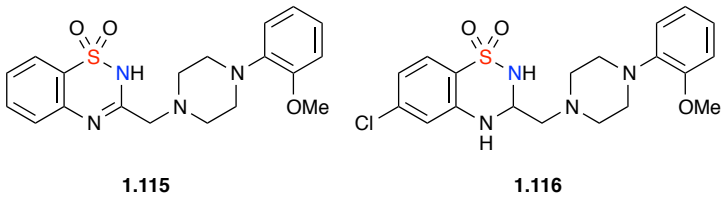
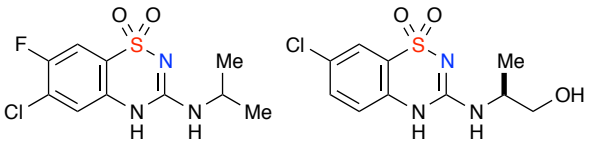


Figure 1.37

A series of 6,7-disubstituted 4*H*-1,2,4-benzothiadiazine 1,1-dioxides involving a short alkylamino side chain in the 3-position were synthesized by de Tullio and coworkers in 2005. All derivatives were examined on rat pancreatic islets and on rat aorta rings.[100] *In vitro* data revealed that, in most substitutions, in the 6-and the 7-positions increased compound activity as inhibitors of insulin secretion, while the myorelaxant potency of the drugs was maintained or enhanced depending on the nature of the substituent in the 7-position. However, compounds with one or two fluorine atoms and a methoxy group in the 7-position, appeared potent and selective inhibitors of insulin release. Radio isotopic and fluorometric experiments with the most potent compound inhibiting insulin release (**1.117**, BPDZ 259, 6-chloro-7-fluoro-3-isopropylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide) confirmed that the drug activated K_{ATP} channels (Figure 1.38). Among them, compound **1.117** was the most potent and selective pancreatic potassium channel opener.

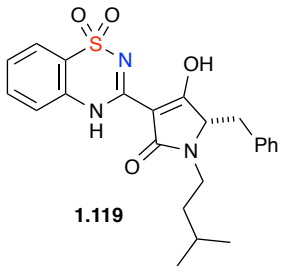
In 2011, de Tullio and coworkers also introduced a hydroxyl group onto the 3-alkylaminoside chain to improve physicochemical and pharmacological properties based on previous observation.[101] The authors evaluated both (*R*) and (*S*) enantiomers for biological activities and (*R*)-7-chloro-3-(1-hydroxy-2-propyl)amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide **1.118** to be the most potent. Compound **1.118** can be considered as a promising lead compound for SUR1-selective K_{ATP} channel openers.



1.117 **1.118**

Figure 1.38

In 2005, Fitch and coworkers synthesized a series of benzothiadiazine-substituted tetramic acid derivatives as potent inhibitors of hepatitis C virus RNA-dependent RNA polymerase.[102] The authors observed that compound **1.119** showed modest but encouraging activity against HCV NS5B polymerase (~3.5 μM), prompting further investigation (Figure 1.39).



1.119

Figure 1.39

In 2011, Kamal and coworkers synthesized a series of [1,2,4]triazolo [1,5-*b*]benzothiadiazine conjugates and evaluated them for their anti-proliferative activities.[103] The compound **1.120** displayed potent cytotoxicity against human leukemia HL-60 cell lines with IC_{50} values in the range of 0.08–0.70 μM (Figure 1.40). The authors also reported the synthesis of a class of arylsulfonamido-conjugated oxazolidinones.[104] Compounds **1.121a** and **1.121b** exhibited good *in vitro* activity against *Mycobacterium tuberculosis* H37Rv. Furthermore, the compound **1.121a** was nontoxic towards human foreskin fibroblast (HFF) cells.

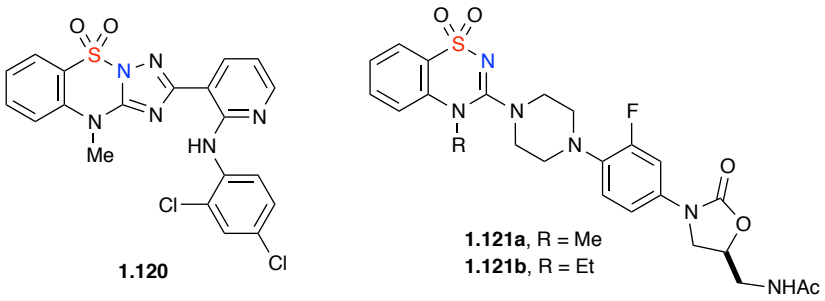


Figure 1.40

In 2008, Francotte and coworkers designed a series of pyrido-[2,3-*e*]-[1,2,4]-thiadiazines ('5-aza' compounds) substituted at the 7-position in order to improve lipophilicity for new positive allosteric modulators of the AMPA receptors based on SAR studies.[105] Among them, compound **1.122,** containing a 7-chloro and N4-ethyl group, showed the most interesting *in vitro* activity with the proper lipophilicity to bind the central nervous system (CNS) (Figure 1.41).

In 2010, Ma and coworkers extended to benzothiadiazine 1,1-dioxide analogues bearing different substituent groups at N2, N4 and 7 positions of the system.[106] The compounds with an N4-acetic acid group and an N2-benzyl group exhibited significant and selective *in vitro* inhibition on aldose reductase (ALR2). In particular **1.123a**, **1.123b**, and **1.123c** showed more pronounced ALR2 inhibitory activities (Figure 1.41). The authors identified that the N4-acetic acid group and N2-benzyl group were recommended for ALR2 inhibitory activity from SAR analysis.

In 2011, Ma and coworkers also synthesized a series of pyrido[2,3-*e*]-[1,2,4]-thiadiazine 1,1-dioxide acetic acid derivatives and tested for inhibitory activities against ALR2.[107] These compounds were identified to be potent aldose reductase inhibitors with IC_{50} values ranging from 0.038 μM to 11.29 μM. Of these

derivatives, compound **1.124** exhibited the highest inhibition activity (Figure 1.41). Structure-activity relationship studies demonstrated that the N2-benzyl group with electron-withdrawing substituents and N4-acetic acid group were essential for in this system.

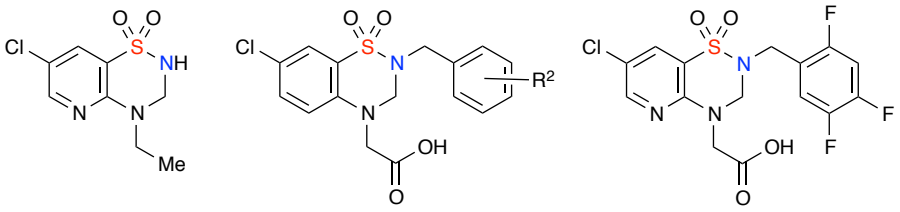


Figure 1.41

Cannazza and coworkers synthesized a series of 5-arylbenzothiadiazine derivatives as positive allosteric modulators of AMPA/Kainate receptors in 2012.[108] During the investigation compounds **1.125** and **1.126** displayed higher activity, plausibly due to H-bond ability within the 5-membered heterocycles (Figure 1.42). The authors also observed that compound **1.125** was more active than compound **1.126** because of the electronegativity difference between the oxygen atom and sulfur atom of the heterocycles.

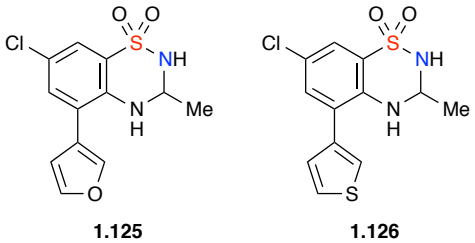


Figure 1.42

1.4.5 4-Hydroxy-2*H*-benzo[*e*][1,2]thiazine 1,1-Dioxide Derivatives

3,4-Dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide α-ketomide compounds are well known as potent calpain I inhibitors. In this regard, 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-one derivatives were synthesized and evaluated by Zia-ur-Rehman and coworkers in 2006.[109] Among the series of compounds, **1.127** displayed better activity against *Escherichia coli* (Figure 1.43). In 2009, the authors also prepared 4-hydroxy-*N'*-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides derivatives and examined them for several antibacterial activities.[110] Compounds **1.128a** and **1.128c** showed significant activities against *S. typhi.* Compound **1.128b** revealed remarkable activity against *S. aureus*.

In 2010, Ahn and coworkers synthesized cyclic sulfonamide derivatives as new 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors (Figure 1.43).[111] Of derivatives tested, compound **1.129** was obtained with good *in vitro* activity and selectivity toward human 11β-HSD1. Interestingly, the same core scaffolds bearing two different ketone moieties at N2 and C3 positions also exhibited a good *in vitro* inhibitory activity.

A series of benzo-thiopyran *S*-dioxides, as exemplified by **1.131**, were discovered from high throughput screening of the Pfizer chemical file against the human mPGES-1 enzyme (Figure 1.43).[112] Based on this bioactivity, in 2010, Wang and coworkers synthesized compound **1.132**. The authors also found potency both in the enzyme and cell-based assays furthermore compound **1.132** exhibited selectivity for mPGES-1 over COX-2. In order to improve biological activity, several analogues

were prepared based on SAR analysis. Compounds with no linker between the C and D rings showed less potency both in the enzyme and cell assay compared with compound **1.132**, and compounds with a single heteroatom linker also displayed decrease enzyme inhibition. Among them, compound **1.130b** showed excellent mPGES-1 inhibition and selectivity over COX-2 in the human fetal fibroblast cell assay. The authors noticed that the acidic proton within the dioxobenzothiazinone is very significant for achieving potent mPGES-1 inhibition. Compound **1.130** also displayed the activity against PGE2 production in the LPS/human whole blood assay with an IC_{50} around 5 μM. The authors explained that this low inhibition in the whole blood assay was due to the high protein binding of the molecule.

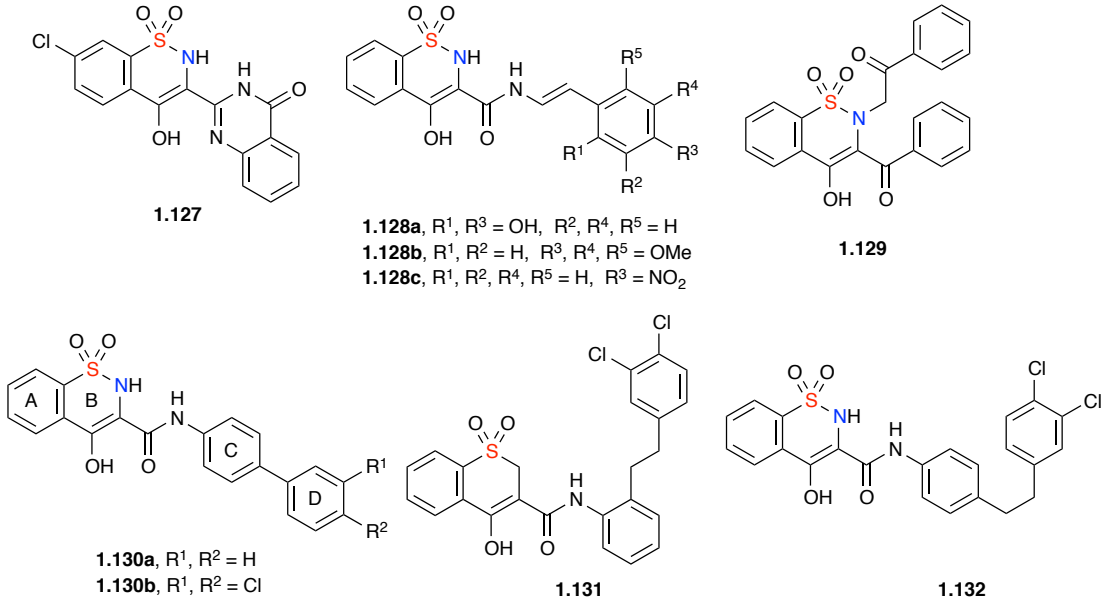


Figure 1.43

1.4.6 Benzothiadiazine-hydroxyquinolin-2(1*H*)-one Derivatives

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and the leading cause of death from liver disease in the United States.[113] The Centers for Disease Control and Prevention estimate that more than 4.1 million individuals in the United States have ongoing HCV infection.[113] The preliminary SAR of the *N*-1-alkyl benzothiadiazines showed equivalent polymerase activity for the quinolone core **1.133** and 1,8-naphthyridone core **1.134** by Pratt and coworkers from Abbott laboratory in 2005 (Figure 1.44).[114] Pratt and coworkers also performed a series of investigations to obtain new inhibitors of HCV NS5B polymerase. During the study, the authors found that the nature of the hydrophobic fragment at the N1 position of the quinolone ring significantly effected potency of biological activity. With this information, the authors designed several types of molecules to improve activities. Among the series of analogues, compounds **1.134** displayed better activity. Introduction of an oxygen or nitrogen atom as a linker (X) in the system could allow the attached alkyl groups to reach to hydrophobic binding via lightly different bond angles and conformations. However none of these analogues showed pronounced improved activity over compounds **1.134**.

In 2006, Rockway and coworkers carried out more detailed investigations on 1,8-naphthyridone core derivatives in order to improve activities.[115] The authors found that a methyl sulfonamide group to the position 7 of the D-ring in substituted *N*-1-3-methylbutyl-4-hydroxy-1,8-naphthyridone benzothiadiazine **1.133**, displayed enhanced enzyme inhibition potency as well as cell culture activity (Figure 1.44).

Furthermore, Rockway and coworkers introduced a sulfamide group to extend more functionality away from the methyl sulfonamide based on the SAR analysis.[116] Compounds **1.139** and **1.140** containing the methyl and unsubstituted benzothiadiazine sulfamides displayed the most potent biochemical and cell culture activities. However, these compounds showed poor solubility.

In 2008, Huchinson and coworkers focused on modifications at C1 of the B ring in the hydroxyquinolon-3-yl-benzothiadiazine series, whereby they substituted a dialkyl naphthalene unit to increase potency.[117] Upon generation of a small set of 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs, the SAR analysis suggested that the most potent analogues bear an unsymmetrical dialkyl groups in the B ring. In addition, Huchinson and coworkers also found that the compounds containing a more polar ester and diol group were less potency. This suggested that the binding pocket in this region is hydrophobic in nature. In general, the saturated alkane analogues were more active than the corresponding unsaturated alkene derivatives. Compound **1.141** showed the most potent activity in the assay as well as better solubility properties than compounds **1.139** and **1.140** (Figure 1.44).

Because compound **1.141** was a racemic mixture, in 2009, Wagner and coworkers synthesized all enantiomerically pure compounds.[118] (*R*)-Configured isomers **1.142a** and **1.142b** were more active stereoisomers than (*S*)-configured compounds from *in vitro* studies. Both compounds **1.142a** and **1.142b** inhibited genotypes 1a and 1b polymerase activity and HCV replicon replication at low nM concentrations. The (*R*)-configured isoamyl and neo-hexyl substituted compounds

1.142a and **1.142b** showed promise as drug candidates for the treatment of HCV infection.

In 2009, Randolph and coworkers reported that the B-ring dialkylthiadiazine inhibitors, containing a variety of substitutions on this site, exhibited low nM inhibitors of genotypes 1a and 1b polymerase.[119] The methyl group of the B-ring was replaced with an amino functionality to improve inhibition ability. The analogue **1.143** bearing neohexyl and benzylamine moieties displayed good pharmacokinetic properties in rat following oral dosing, with an oral bioavailability of 56%.

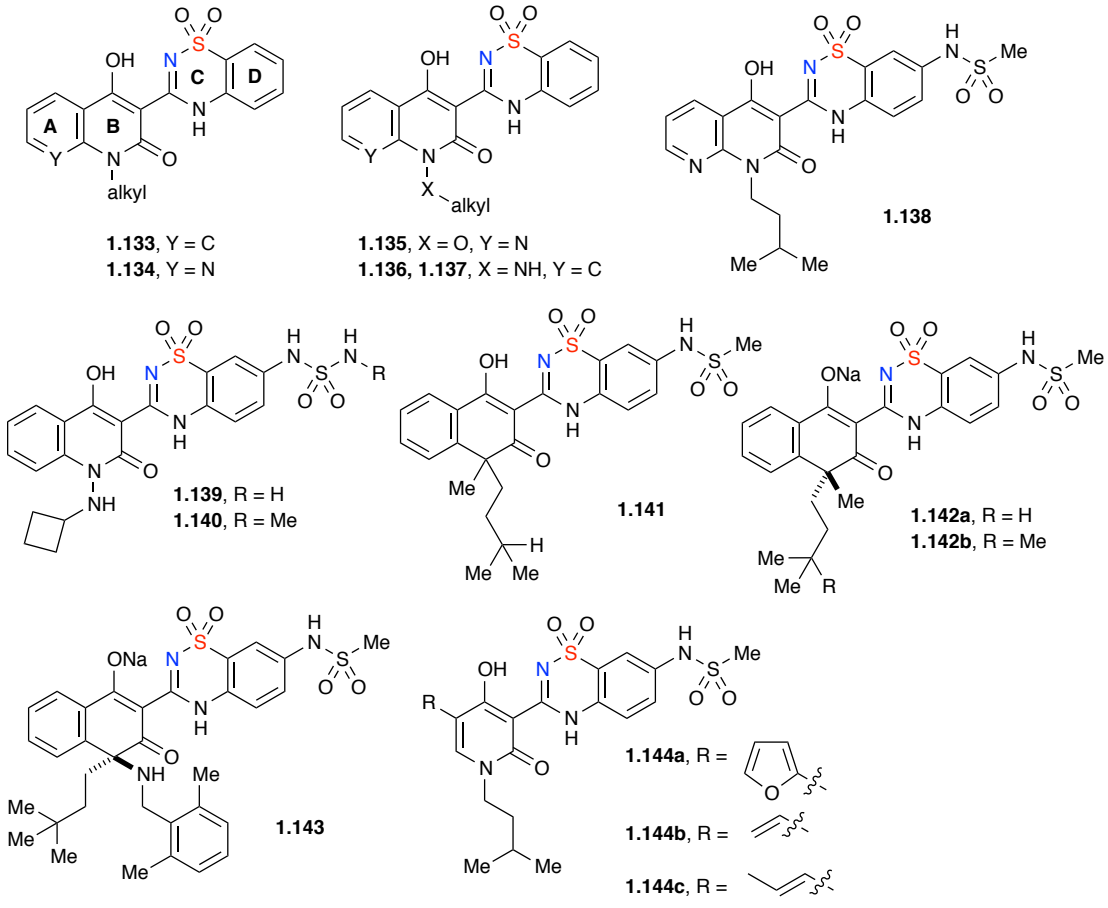


Figure 1.44

In 2008, Donner and coworkers noticed that the tetracyclic benzothiadiazine system has a major drawback due to its high degree of protein binding. In order to solve this problem, Donner and coworkers studied the possibility of replacement of this four-ring system to the minimum core required for activity.[120] Donner and coworkers found that when the A-ring was removed, the potency of compound decreased and substitutions from the B-ring into the space previously occupied by the A-ring produced analogues that retained nM enzyme inhibitory potency. Several three-ring systems, namely **1.144a**, **1.144b** and **1.144c**, bearing small substituents to the 5-position of the B-ring displayed more active in 1b replicon than the original tetracyclic analogues.

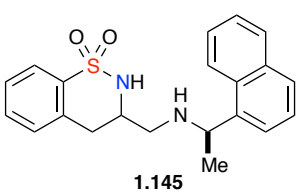
1.5 Bioactive Compounds Containing 7-Membered Sultam Moiety

1.5.1 Benzothiazepine 1,1-dioxide Derivatives

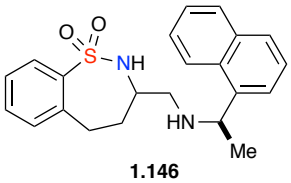
In 2010, Dodd and coworker synthesized several benzofused sultam compounds as potential calcium sensing receptor agonists.[121] The corresponding compounds were examined for agonist activity on human CaSR (hCaSR) expressed in HEK293 cells. Among them, the six- and seven-membered cyclic sulfonamide derivatives **1.145** and **1.146** were the most potent calcimimetics. Even though the calcimimetic activities of both compounds were less active than that of calindol, these lead candidates allow achieving diverse structural modifications for better activities.

In 2003, 5-aryl-3,3-dibutyl-7-(dimethylamino)-1,2-benzothiazepin-4-ol 1,1-dioxide derivatives were prepared by Tollefson and coworkers as potential apical

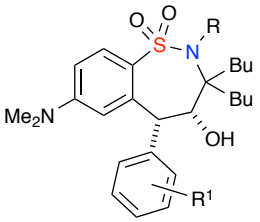
sodium co-dependent bile acid transporter (ASBT) inhibitors.[122] The authors found that compounds **1.147a**, **1.147c** and **1.147d** revealed low nM *in vitro* activity and inhibited ASBT for the potential treatment for hyperlipidemia (Figure 1.45). In particular, compound **1.147b** exhibited the most potent activity.



1.145



1.146



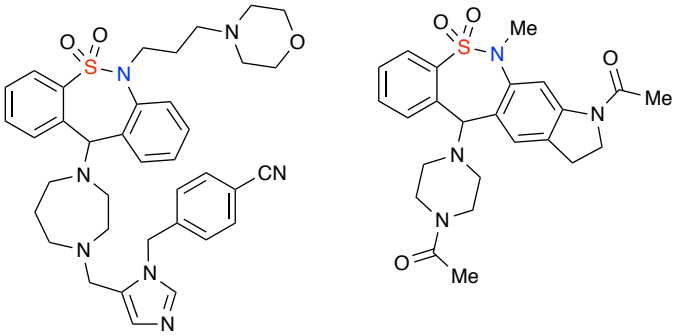
	R	R^1
1.147a	H	4-$((OCH_2CH_2)_3N^+Et_3)I^-$
1.147b	H	3-$(NHCO(CH_2)_4N^+Et_3)CF_3CO_2^-$
1.147c	Me	4-$((OCH_2CH_2)_3(N^+C_5H_4))I^-$
1.147d	Me	4-$((OCH_2CH_2)_3N^+Et_3)I^-$

Figure 1.45

In 2007, Millet and coworkers synthesized a series of tricyclic-containing dioxodibenzothiazepine or dibenzocycloheptane derivatives as farnesyltransferase (FTase) inhibitors.[123] These compounds were evaluated for their *in vitro* inhibitory activity against FTase using the continuous fluorescence spectrometry technique. Among the series of compounds, dioxodibenzothiazepine **1.148** revealed pronounced inhibitory FTase activity (IC_{50} = 17.3 nM) and antiproliferative properties (Figure 1.46). The authors observed that the compound containing an additional morpholine moiety as a hydrogen bond acceptor resulted in improved binding to the enzyme.

In 2005, Depreux and coworkers prepared a series of benzoindolinothiazepines involving a piperazine fragment with interesting cytostatic properties.[124] The authors observed that compound **1.149** was an inhibitor of PC3

proliferation (IC_{50} = 0.19 μM) (Figure 1.46).



1.148 **1.149**

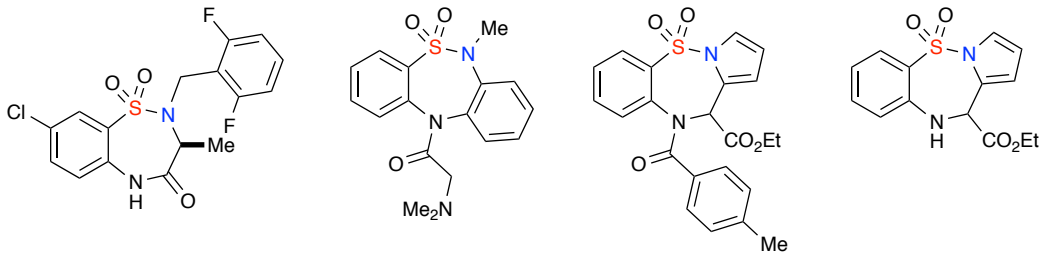
Figure1.46

1.5.2 Benzothiadiazepine 1,1-Dioxide Derivatives

Several compounds including nevirapine, efavirenz (Sustiva), and delavirdine (Rescriptor) have been approved for clinical use as AIDS therapeutics[125] prompting Di Santo and coworkers in 2006 to report the first example of 1-[(2-hydroxyethoxy)methyl]-6-phenylsulfanyl)thymine (HEPT) and 4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and -thione (TIBO) derivatives within the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of chemotherapeutic agents for the treatment of AIDS. The novel TIBO- and TBO-like derivatives were prepared and evaluated for their cytotoxicity and anti-HIV-1 activity in MT-4 cells. These compounds revealed activities against the HIV-1 replication cycle in cell-based assays. In particular, compound **1.150** was the most potent in cell-based assays (EC_{50}= 0.07 mm, CC_{50}>200 mm, SI>2857) and also showed more selectivity than a reference drug (Figure 1.47).

In 1991, Giannotti and coworkers synthesized a family of 11-[(aminoalkyl)carbonyl] derivatives of 6,11-dihydrodibenzo[*c*,*f*][1,2,5]thiadiazepine 5,5-dioxide for potential antidepressant activity in the apomorphine-induced hypothermia (Apo 16).[126] Compound **1.151** showed not only structural similarities with classical antidepressant tricyclic compounds, but was also the most potent and least toxic in this series, by assessing physostigmine lethality (Figure 1.47).

Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (PBTD) derivatives were introduced for apoptosis in human breakpoint cluster region (BCR)-Abelson murine leukemia (ABL) expressing leukemia cells, by Silvestri and coworkers in 2006.[127] Based on the apoptotic mechanism studies, the authors found that compounds **1.152** and **1.153** activated caspase activity and induced apoptosis before the BCR-ABL protein expression (Figure 1.47). Silvestri and coworkers obtained PBTD derivatives as a new class of valid candidates for the treatment of chronic myelogenous leukemia (CML).



1.150 **1.151** **1.152** **1.153**

Figure 1.47

In 2005, a series of benzopyridothiadiazepine derivatives were synthesized and tested for their anti-proliferative activity toward the murine L1210 leukemia cell line by Lebegue and coworkers.[128] Several compounds displayed submicromoloar

cytotoxicity. In particular compounds **1.154** and **1.155**, were the most potent inhibitors of tubulin polymerization with IC_{50} of 3.8 and 2.4 μM respectively, compared to 2.4 μM for desoxypodophyllotoxin (Figure 1.48). The 4-methoxyphenylethyl group on the pyridinyl nitrogen of the benzopyridothiadiazepine was required for the antiproliferative activity. Benzopyridothiadiazepine dioxides were considered as a promising new class of tubulin binders due to the *in vitro* activities of compounds **1.154** and **1.155**.

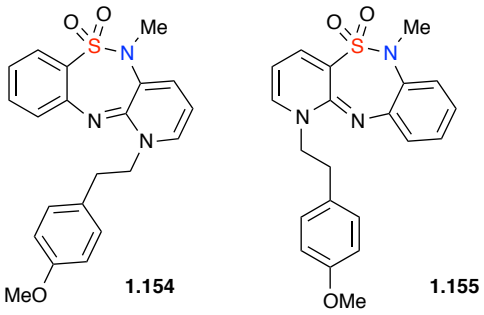


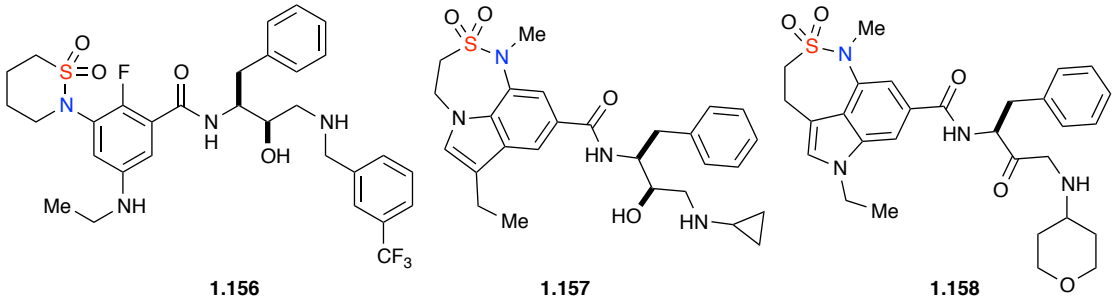
Figure 1.48

1.5.3 Thiadiazepinoindole 2,2-Dioxide Derivatives

In 2009, Demont and coworkers synthesized a series of hydroxyethylamines derivatives, as beta-secretase 1 (BACE-1) inhibitors, with μM potency in cell-based assays.[129] Among them, GSK188909 (compound **1.156**) possessed appropriate pharmacokinetics and was the first orally bioavailable inhibitor reported to demonstrate brain amyloid lowering in an animal model (Figure 1.49).

In 2008 Demont and coworkers, reported another type of sultam compounds as BACE-1 inhibitors.[130] The compound **1.157** revealed nM potency in a cellular

assay as well as enhanced oral bioavailability in rat and good bioavailability in dogs. The authors extended their work to synthesize 6-membered sultam as well as tricyclic sultam compounds based on previous observations of the first generation of hydroxyethylamine BACE-1 inhibitors.[131] Several compounds displayed having good oral exposure from *in vivo* pharmacokinetics profile in rat as well as dog. Generally, compounds in the tricyclic series need to contain a basic nitrogen in order to obtain good correlation of activities. The α-amino ketone derivative **1.158** was the first tricyclic BACE-1 inhibitor without hydroxyethylamine transition state mimetic that displayed excellent potency in cell-based assays. During the investigation, inhibitors containing [8.6.5]-tricyclic system were also prepared, however, these inhibitors decreased potency and selectivity when compared to their [7.6.5] counterparts.[132]



1.156 **1.157** **1.158**

Figure 1.49

1.6 Conclusions

There are several commercially available drugs containing sultam moiety in order to treat different types of diseases. Sultam compounds involving different ring

size and connectivity have been reported possessing a variety of biologically activities such as anti-HIV, HCV-NS5B polymerase and HIV-1 integrase activities. In this regard, developments of new chemical methodologies to generate more skeletally diverse sultam derivatives are important to survey more biologically active sultam-containing compounds.

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Chapter 2

Metathesis Cascade Strategies (ROM–RCM–CM):

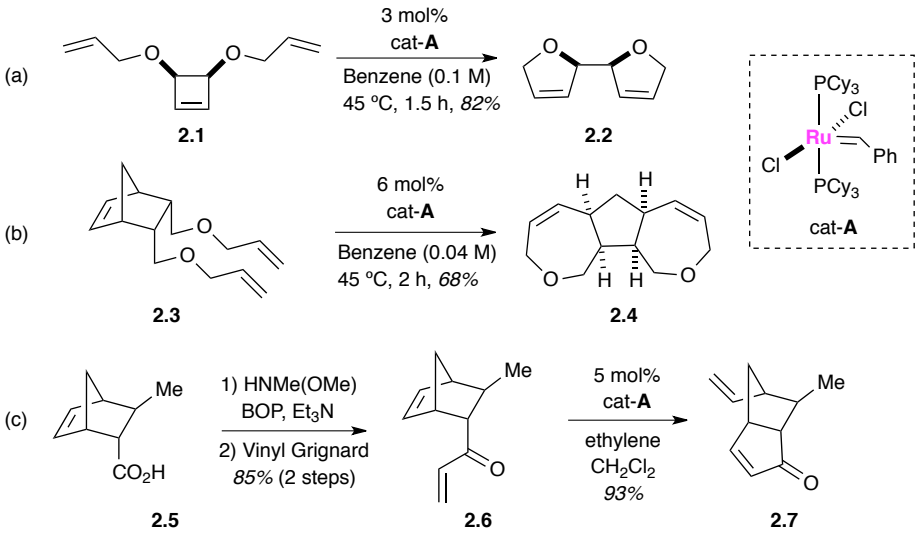
A Diversity-Oriented Approach to Skeletally Diverse Sultams

2.1 Introduction

2.1.1 Metathesis Reaction in Diversity-Oriented Synthesis

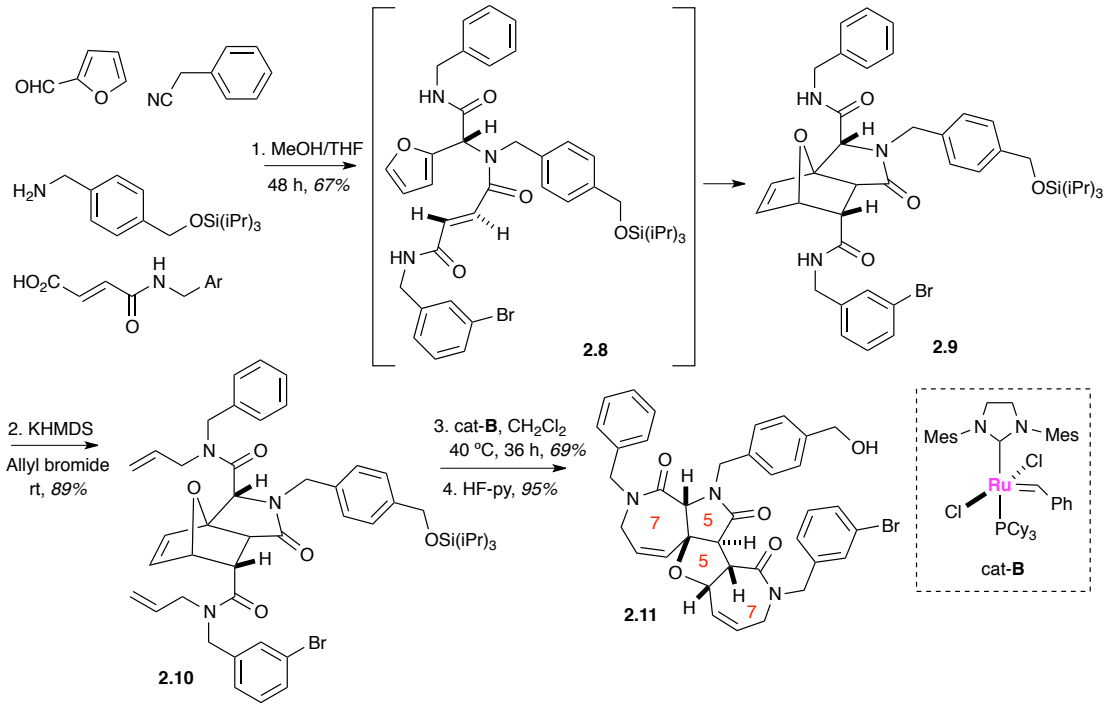
The development of new chemical methods to generate novel small molecules with diverse structures to probe chemical space is an important aspect of early phase drug discovery. Diversity-oriented synthesis (DOS) is one of the most powerful methods to produce structurally complex and skeletally diverse small molecules.[1] As collections of small molecules can represent a wide range of physical and biological properties, and they are ideal synthetic target to aspire in order to probe chemical space for the identification of novel lead compounds in early stage drug discovery.[2] Towards this goal, the development of simple methods that, allow for the production of an array of structurally complex scaffolds is one of several challenging facets of DOS. A number of accomplished strategies have reported employing skeletal rearrangement utilizing both functional-group-pairing (FGP)[1d,3] strategies and tandem metathesis (TM) strategies.[4]

In 1996, Grubbs and coworkers reported a tandem ring opening-ring closing metathesis (RO–RCM) strategy, that allowed access to a number of bi- and tricyclic compounds from their strained mono- and bicyclic precursors in good to excellent yields [Scheme 2.1 (a) and (b)].[5a] In 2004, Aubé and coworkers also reported an RO–RCM reaction protocol, mediated by Grubbs first generation catalyst, en route to the total synthesis of dendrobatid alkaloids [Scheme 2.1 (c)].[5b]



Scheme 2.1 *Representative ROM–RCM reaction strategy.*

Recently, a number of strategies employing ROM–CM strategies with norbornene, oxa-norbornene, and aza-norbornene derivatives have been reported.[6] In particular, a number of key metathesis cascades and strategies have surfaced, some in the context of DOS.[7] For example, Schreiber and coworkers reported the efficient synthesis of structurally complex compounds.[7k] A 4-component Ugi reaction and subsequent intramolecular Diels–Alder (IMDA) reaction afforded corresponding tricyclic compound **2.9** via intermediate **2.8**. When treated with Grubbs 2nd generation catalyst {[(IMesH$_2$)(PCy$_3$)(Cl)$_2$Ru]CHPh, (cat-**B**)}[8] allylation product **2.10** readily underwent ROM–RCM (69%), and successive TIPS-deprotection with HF-pyridine produced [7.5.5.7]-tetracyclic compound **2.11** (Scheme 2.2).

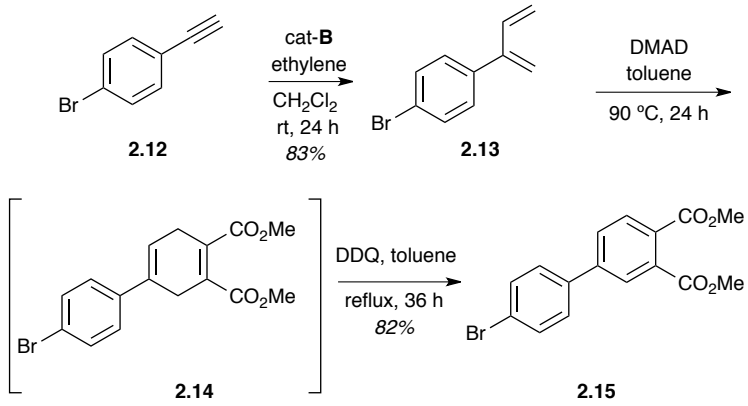


Scheme 2.2

In 2011, Kotha and coworker reported the synthesis of various biaryl compounds using a cross-enyne metathesis strategy in DOS (Scheme 2.3).[9] In the presence of cat-**B**, Substituted phenylacetylene **2.12** underwent cross-enyne metathesis with ethylene to furnish diene **2.13**. Diene **2.13** was then subjected to Diels-Alder reaction conditions to afford the corresponding adduct **2.14**. Finally, aromatization using DDQ provided biaryl compound **2.15** in excellent overall yield (Scheme 2.3).

With the goal of aspiring to the aforementioned attributes of scaffold production, we envisioned a DOS approach, whereby skeletally diverse sultam scaffolds could be generated using a domino ring-opening metathesis/ring-closing metathesis/cross-metathesis (ROM–RCM–CM) cascade sequence with a readily

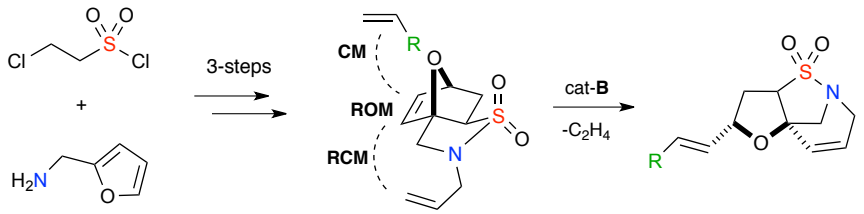
derived oxa-norbornenyl sultam.



Scheme 2.3

Sulfonamides and unnatural sultams (cyclic sulfonamides) have been reported as privileged structures in drug discovery due to their diverse biological properties. A number of reports have highlighted an assortment of sultams that display potent activity against a variety of targets, including inhibition of COX-2 (Ampiroxicam),[10,11] HIV integrase,[12] and cysteine protease involved in the progression of malaria,[13] and inhibition of matrix metalloproteinase (MMP)[14] and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.[15]

In this investigation, we explored the application of an ROM–RCM–CM strategy for the generation of a collection of skeletally diverse sultams via a diastereoselective intramolecular Diels–Alder (IMDA) reaction with a central norbornenyl sultam core (Scheme 2.4).



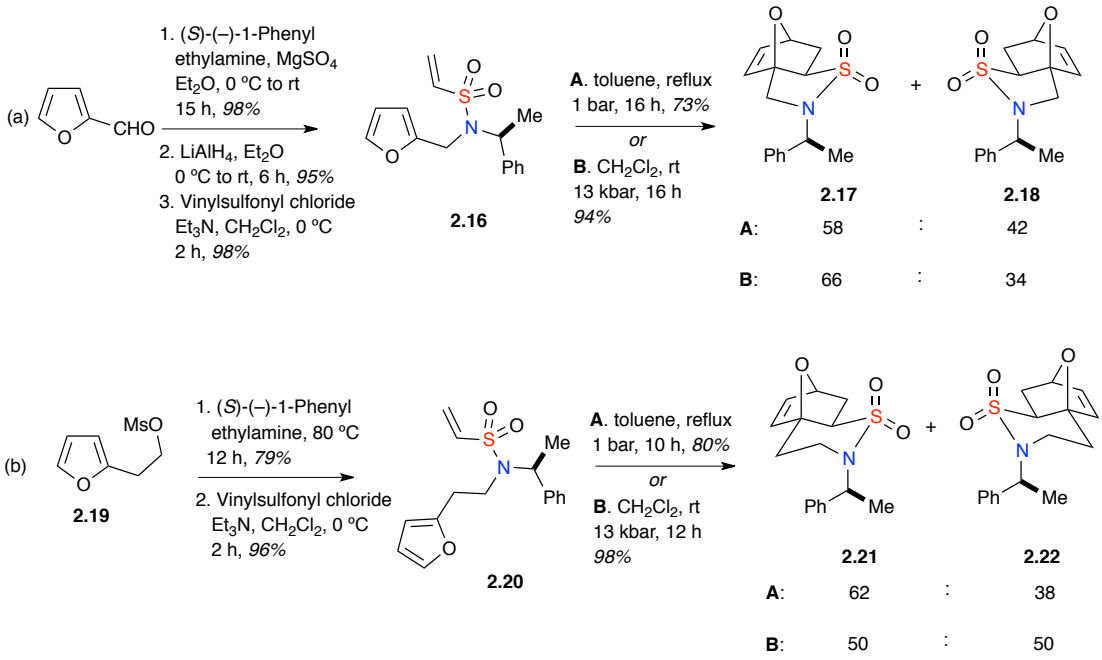
Scheme 2.4 *ROM–RCM–CM strategy.*

A number of transition metal-catalyzed approaches to sultams have come to light, including ring-closing metathesis (RCM).[16] Our continued interest in the development of new synthetic routes toward structurally diverse sulfur-containing small molecules for library production[16,17] has prompted the following investigation on the application of metathesis cascade processes for their construction.

2.2 Results and Discussion

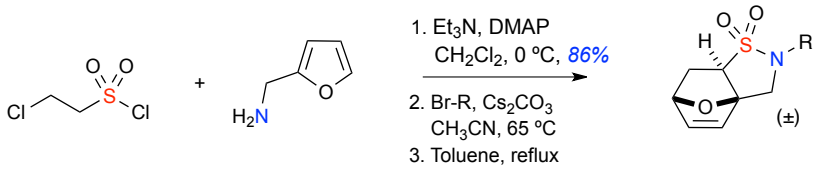
2.2.1 Intramolecular Diels-Alder Reaction

As developed by Metz and coworkers in 1989, the IMDA reaction of both vinyl sulfonates[18] and vinyl sulfonamides[19] with substituted furans has provided an efficient route to highly versatile intermediates rich in stereochemistry and functionality. In their seminal paper, Metz *et al.* report furan-containing vinyl sulfonamide **2.16** was derived from commercially available starting material in 3 steps. Vinyl sulfonamide **2.16** underwent IMDA reaction to produce readily separable *exo*-*γ*-sultam compounds **2.17** and **2.18** [Scheme 2.5 (a)]. Production of the *exo*-*δ*-homologues **2.21** and **2.22** occurred via furan derivative **2.19** in 3 steps [Scheme 2.5 (b)].



Scheme 2.5

Norbornene systems of this type possess a strained internal double bond, and thus are attractive scaffolds for application of the aforementioned metathesis cascade process. Utilizing a similar IMDA method, the IMDA-derived sultams **2.23** and **2.24** were synthesized from commercially available starting materials.[19]



2.23, R = Allyl, *55%* (over 2 steps)
2.24, R = Propargyl, *58%* (over 2 steps)

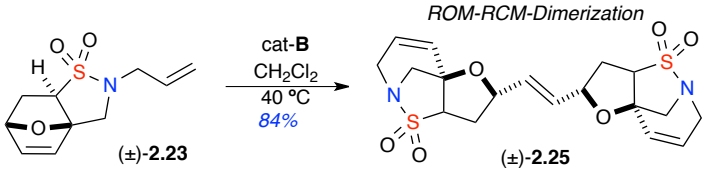
Scheme 2.6

2-Chloroethanesulfonyl chloride was coupled with furfurylamine under standard conditions to obtain the corresponding sulfonamide in 86% yield. Allylation/propargylation of the resulting sulfonamide, followed by *in situ* IMDA

reaction in reflux conditions, furnished the corresponding tricyclic sultams **2.23** and **2.24**, in 55% and 58% yields, respectively (Scheme 2.6), as single diastereomers.

2.2.2 ROM–RCM–CM Strategy to a Tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole 1,1-Dioxide Sultams

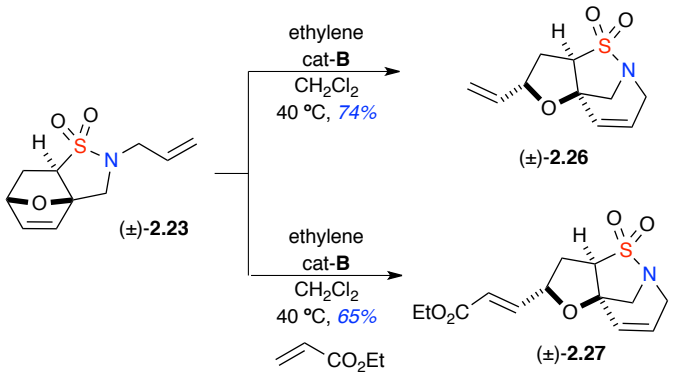
Application of the proposed ROM–RCM–CM cascade protocol was explored with scaffold **2.23**. Sultam **2.23** was subjected to 5 mol % of cat-**B**, at 0.005 M in CH_2Cl_2 at 40 ºC under argon atmosphere for 3 hours, to provide ROM–RCM–dimerization product **2.25** in 84% yield (Scheme 2.7). In order to prevent homodimerization process, a cross-metathesis partner was used to afford the desired product. Additionally, the utilization of ethylene gas has been well reported in the application of ROM–RCM–CM, whereby a terminal olefin is ultimately produced.[7]



Scheme 2.7

Thus, sultam **2.23** was subjected to standard cascade conditions under ethylene atmosphere, in ethylene-degassed CH_2Cl_2 solvent. The corresponding tricyclic sultam **2.26** containing a terminal olefin was obtained, in 74% yield with ethylene acting as the final cross-metathesis partner. Based on this result, studies were directed toward the addition of a cross-metathesis partner to circumvent dimerization and incorporate an additional point of diversity. When sultam **2.23** was

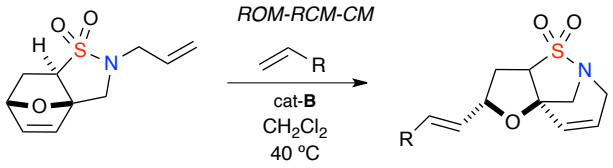
subjected in the presence of ethyl acrylate [10 equiv], cat-**B** [10 mol%], in 0.005 M CH_2Cl_2 at 40 ºC, the desired bridged tricyclic sultam **2.27** derived from ROM–RCM–CM process was isolated in 65% yield (Scheme 2.8).

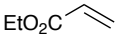
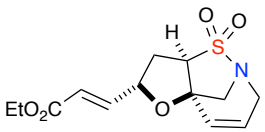
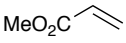
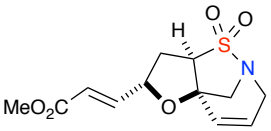
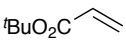
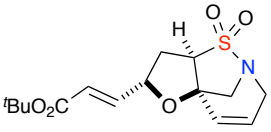
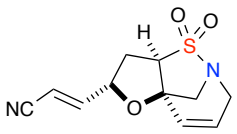
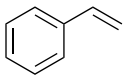
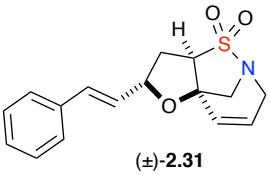
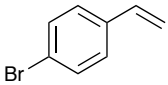
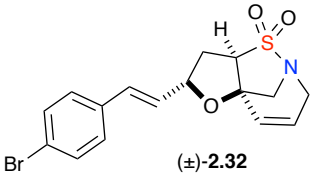


Scheme 2.8

With the successful application of an ROM–RCM–CM protocol, the scope of possible cross-metathesis partners was studied. When exposed to the aforementioned protocol, a variety of acrylate, including ethyl acrylate, methyl acrylate and *tert*-butyl acrylate, were converted to the desired products with good yield (Entries 1–3, Table 2.1). Interestingly, the application of methyl vinyl ketone (MVK) did not provide the desired product. In addition to acrylates, acrylonitrile and styrene were applied as the cross-metathesis partners. Under standard cascade reaction conditions, the protocol provided the desired tricyclic sultam products as the sole product in good isolated yields (Entries 4–6, Table 2.1).

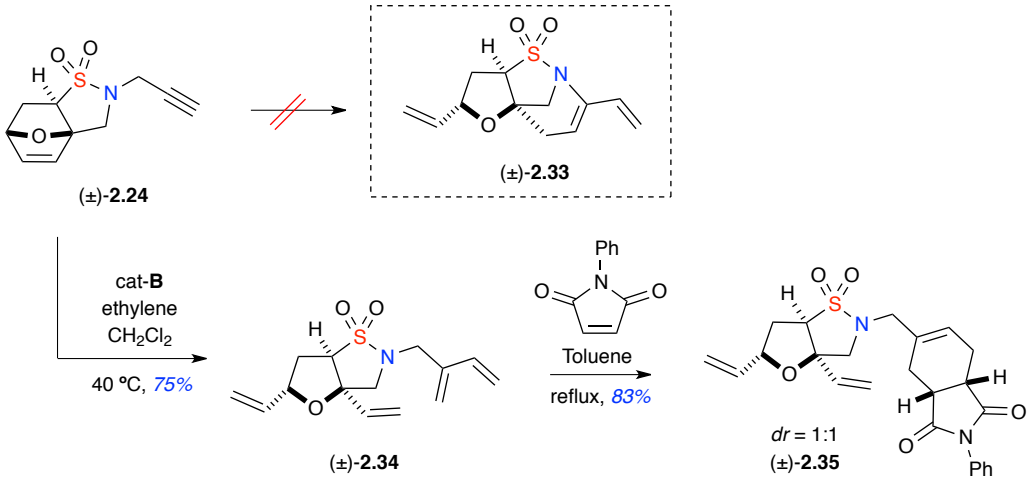
Table 2.1.



Entry	Cross-Partner	Product	Yield
1		 (±)-**2.27**	65%
2		 (±)-**2.28**	56%
3		 (±)-**2.29**	78%
4		 (±)-**2.30**	81%
5		 (±)-**2.31**	80%
6		 (±)-**2.32**	67%

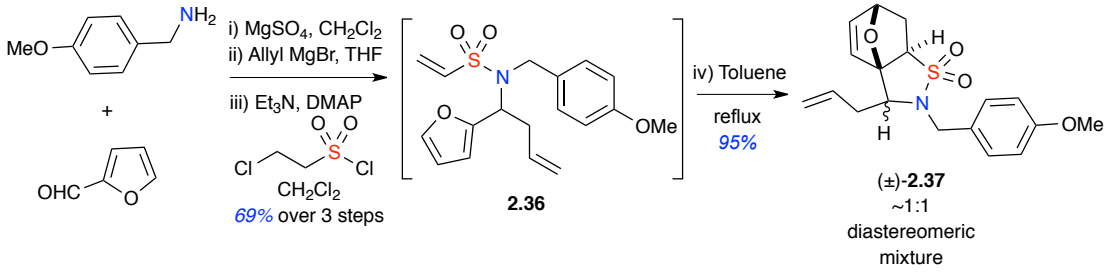
With the aforementioned results in hand, we investigated the metathesis

cascade reaction strategy for the propargyl-substituted sultam **2.24**. In this case, a ring-opening metathesis/ring-closing enyne metathesis/cross metathesis (ROM–RCEM–CM) sequence was envisioned as a method of generating skeletally diverse sultams. Additionally, reaction of sultam **2.24** containing propargyl group in the presence of ethylene would provide the desired product **2.33** bearing a diene fragment, allowing for additional incorporation of diversity via [4+2]-cycloaddition with activated dienophiles under standard reaction condition. However, when sultam **2.24** was subjected to the ROM–RCEM–CM conditions, none of the desired product was observed, instead bicyclic, tetraene-containing sultam **2.34** was obtained in 75% isolated yield. This result showed that sultam **2.24** undergoes an intermolecular enyne metathesis with ethylene instead of the corresponding intramolecular process. Sultam **2.34** bearing tetraene, treated with *N*-phenylmaleimide in toluene at heating condition to provide the corresponding [4+2] *cis*-cycloadduct **2.35** in 83% yield as an inseparable, 1:1 mixture of diastereomers (Scheme 2.9).[20]



Scheme 2.9

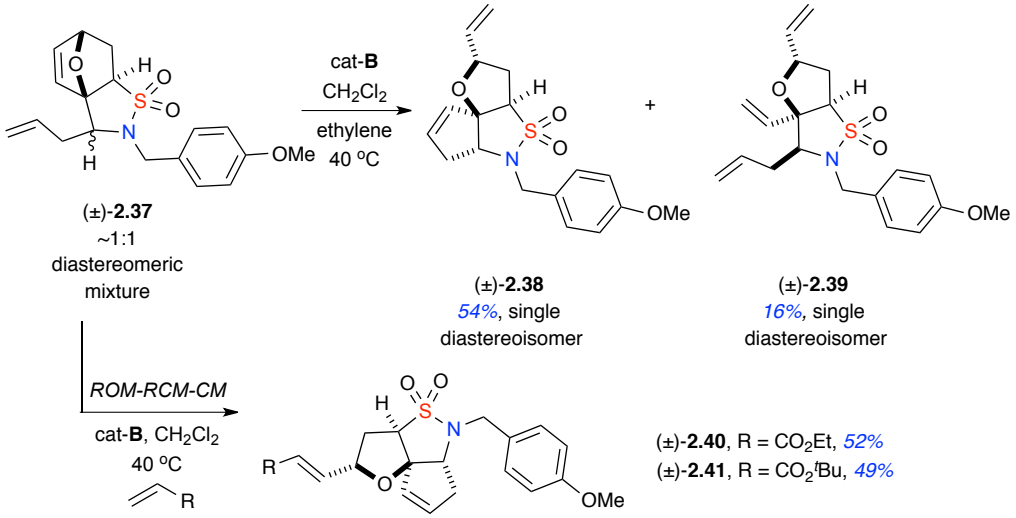
We also investigated the synthesis of a modified sultam scaffold with the simple relocation of the allyl group in **2.23** by adding one carbon that would allow for the generation of new tricyclic sultams **2.37**–**2.39**. This sultam homologue, possessing a tethered allyl group, also enhances overall structural diversity by yielding a different type fused-ring system. 4-Methoxybenzylamine was condensed with 2-furaldehyde to produce the corresponding imine, which was subsequently converted to the furfuryl-substituted allylamine upon the addition of allyl magnesium bromide. Vinyl sulfonylation with 2-chloroethanesulfonyl chloride generated, the corresponding vinyl sulfonamide intermediate **2.36**, which when refluxed in toluene for 12 hours furnished the desired IMDA-derived sultam scaffold (**2.37**) as a mixture of diastereomers (~1:1) in 95% isolated yield (Scheme 2.10).[21]



Scheme 2.10

The diastereomeric mixture of sultam **2.37** was subjected to the ROM–RCM–CM reaction conditions, in the presence of ethylene, to produce two different sultam products, **2.38** and **2.39** (Scheme 2.11). Structures of sultams **2.38** and **2.39** were confirmed by spectroscopic analysis including ^{1}H NMR NOESY studies. These results indicated that diastereomer sultam **2.37a** selectively underwent cyclization to produce the *cis*-fused tricyclic sultam **2.38**. A small amount of bicyclic sultam **2.39**

was also derived from ROM–CM of diastereomer **2.37b** with ethylene.



Scheme 2.11

This result demonstrated that in the case of diastereomer **2.37b**, an unfavorable interaction between the allyl substituent and the *oxo*-bridge prevents proper alignment between the ruthenium alkylidene and the norbornenyl olefin, thus preventing metathesis reaction (Figure 2.1).

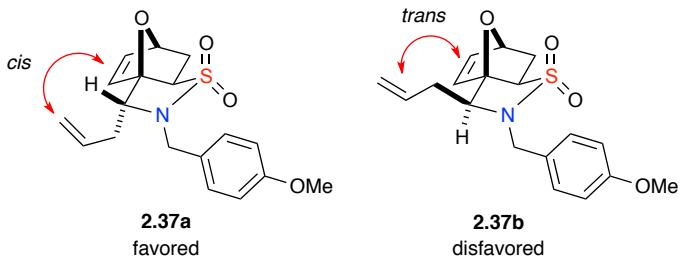
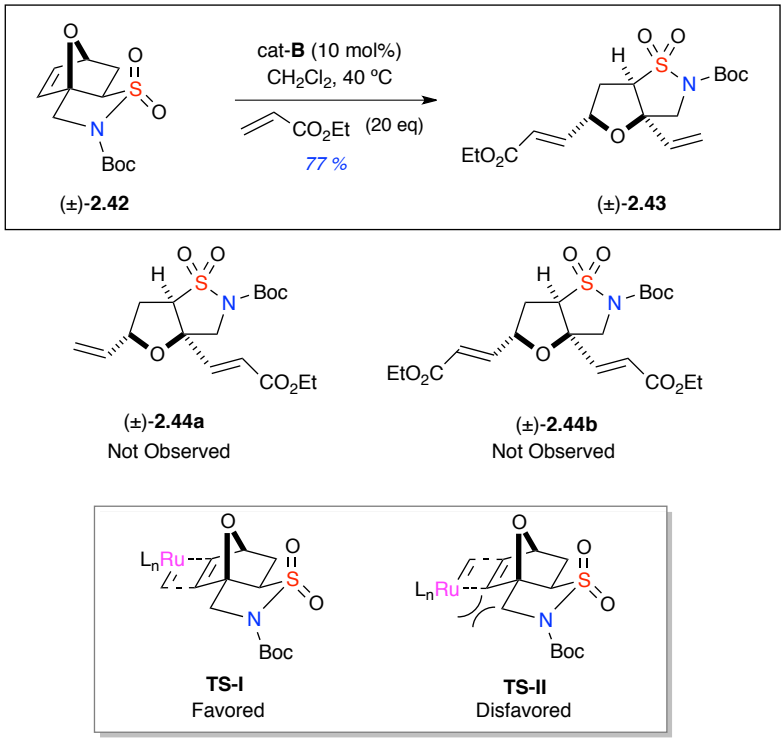


Figure 2.1

Based on this steric effects, the corresponding ROM–RCM–CM product of **2.39** would have a *trans* ring junction in a bicyclo[3.3.0] ring system, which, under the reversible conditions of the reaction, would most likely be disfavored. The ROM–

RCM–CM process with diastereomeric mixture of sultam **2.37**, in the presence of ethyl acrylate or *tert*-butyl acrylate as cross-metathesis partners, provided the desired bridged tricyclic sultams **2.40** and **2.41** in 52% and 49% isolated yields, respectively (Scheme 2.11).

Furthermore, we decided to investigate the rationalization for obtaining one regioisomer product from the ROM–RCM–CM reaction protocol. Boc-protected IMDA sultam **2.42** was subjected to standard reaction conditions with ethyl acrylate as a cross-metathesis partner (Scheme 2.11). This reaction provided only bicyclic sultam **2.43** that was derived from the ROM–CM process and neither **2.44a** nor **2.44b** was observed ultimately. Based on this result, we hypothesized that, upon initiation with ruthenium catalyst, two possible transition states are formed: TS-I and TS-II, where, the TS-I is more favored than the TS-II due to an unfavorable steric interaction between the ligand of the ruthenium catalyst and the carbon backbone of the 5-membered sultam (Scheme 2.12).

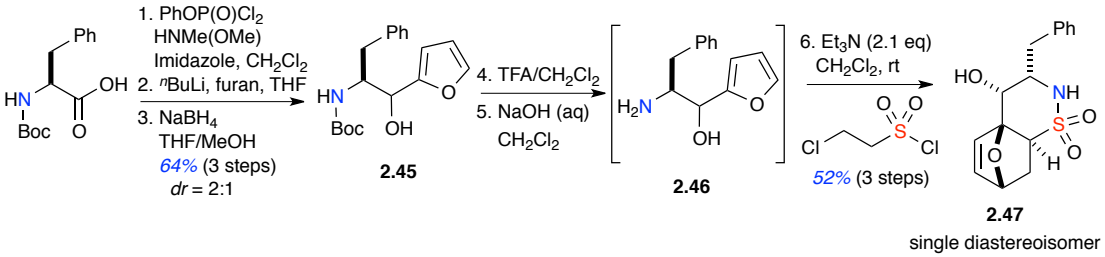


Scheme 2.12

2.2.3 ROM–RCM–CM Strategy to a Hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazine 1,1-Dioxide Sultams

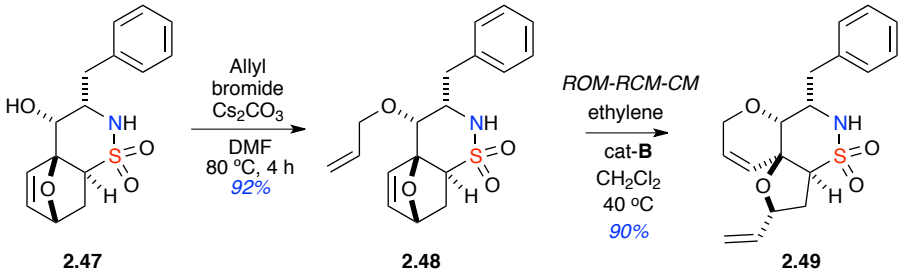
In conjuction with the previously described 5-membered systems, we were also developing the synthesis of an IMDA-derived 6-membered sultam **2.47** involving additional functional handles and therefore proving its utility in the metathesis cascade protocol. In this regard, *N*-Boc-phenylalanine was converted to the corresponding Weinreb amide and reacted with lithiated furan. The furyl ketone treated with $NaBH_4$ to obtain corresponding *N*-Boc-amino alcohol **2.45** as a mixture of diastereoisomers (~2:1) in 64% yield over three steps.[22] An amino alcohol **2.46** as a crude mixture derived from deprotection of the Boc group underwent

sulfonylation/diastereoselective IMDA sequence to afford tricyclic sultam **2.47**, as a single diastereoisomer, in 52% yield over three steps (Scheme 2.11).[19]



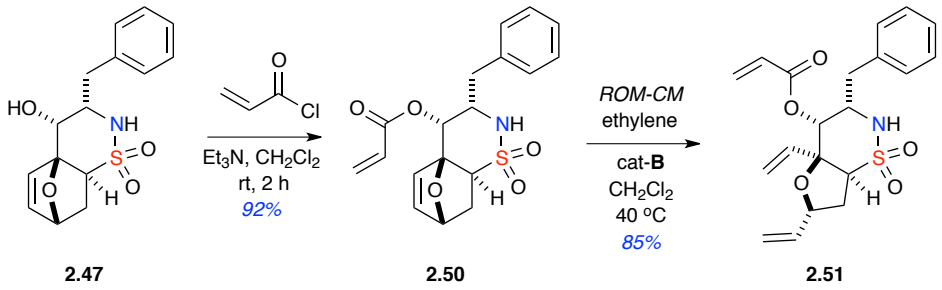
Scheme 2.13

Ticyclic sultam **2.47** is a useful scaffold because of a number of characters in a DOS aspect, including (i) stereochemistry (ii) the presence of both free hydroxy (OH) and free sulfonamide (NH) groups, (iii) peripheral functionality and, (iv) structural rigidity. These features allow for the production of focused libraries to probe chemical space via two approaches. The first is via simple peripheral diversification and the second achieves skeletal diversity utilizing the aforementioned ROM–RCM–CM cascade protocol. Sultam **2.48** derived from chemoselective *O*-allylation reaction of sultam **2.47**,[23] underwent ROM–RCM–CM process to provide desired tricyclic sultam **2.49** in 90% isolated yield (Scheme 2.14).



Scheme 2.14

After acryloylation of sultam **2.47**, the sultam intermediate **2.50** was also converted to bicyclic sultam **2.51** via ROM–CM reaction (Scheme 2.15). Both pathways for IMDA sultam **2.47**, possess another functional handle (SO_2NH) for late stage peripheral diversification. Depending on the property of the olefin appendage in sultam **2.47** it allows us to generate skeletally diverse sultams either tricyclic sultam **2.49** or bicyclic sultam **2.51**, presumably due to variable olefin reactivity types (I, II, II or IV), as defined by Grubbs affecting the site of the initial metathesis event.[24] Overall, the three starting material sultams **2.23**, **2.37**, and **2.47** are tricyclic, IMDA-derived scaffolds that, upon submission to the metathesis cascade protocol generate skeletally diverse [6.6.5] or [6.5.5] fused-ring sultam systems.



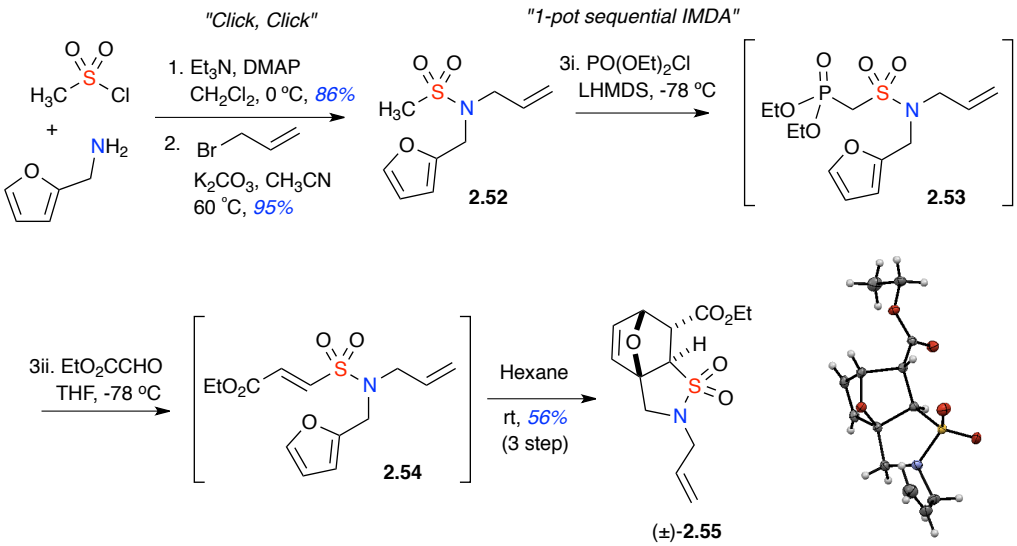
2.47 **2.50** **2.51**

Scheme 2.15

2.2.4 ROM–RCM–CM Strategy to a Functionalized Tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole 1,1-Dioxide Sultam

In the final example, we investigated that the synthesis of a sultam scaffold bearing an ester functional handle as an alternative strategy toward the synthesis of functionalized derivatives of **2.23**. This goal could be achieved via incorporation of the ester moiety in the dienophile component of the IMDA protocol, as reported by

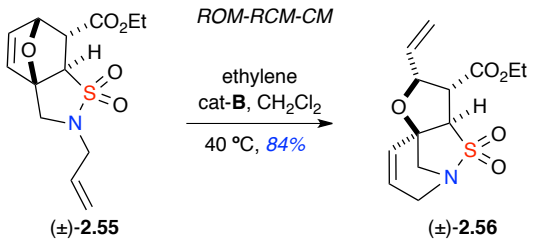
Overman and coworkers in 1999.[25] To this study, furfurylamine was coupled with methanesulfonyl chloride to obtain secondary sulfonamide, then subsequently allylated to yield tertiary sulfonamide **2.52** in 82% over two steps. Generation of the phosphonate **2.53**, followed by Horner–Wadsworth–Emmons reaction with ethyl glyoxalate, provided a mixture of uncyclized sulfonamide **2.54** and IMDA-derived sultam **2.55** after purification to remove any remaining starting material. Addition of hexane to the crude mixture resulted in the sole precipitation of **2.55** as X-ray quality crystals (Scheme 2.16).



Scheme 2.16

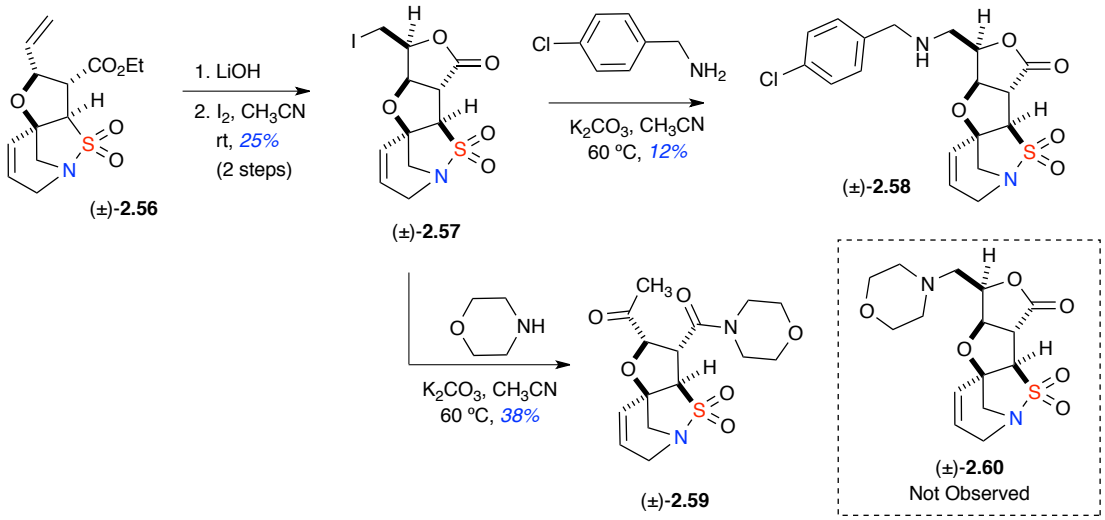
It is important to mention that it was observed that in NMR solvents including $CDCl_3$ and MeOH-d_4, sultam **2.55** undergoes retro-IMDA to generate sultam **2.54** over time.[26] The acidic nature of the solvent catalyzed the retro-IMDA reaction indicates the increased reactivity of the bridged tricyclic system in comparison to sultams **2.54** and **2.55**. Sultam **2.55** was subjected to the metathesis cascade reaction

in the presence of ethylene and cat-**B** in CH_2Cl_2 to produce the desired tricyclic sultam **2.56** bearing an ester group (Scheme 2.17).



Scheme 2.17

Formation of an additional lactone ring was also carried out using iodolactonization reaction between the carboxylate resulting from saponification of the ester with LiOH and the terminal olefin in the presence of iodine to afford tetracyclic, iodo-product **2.57** as a single isomer, albeit in low yield (Scheme 2.18).



Scheme 2.18

The iodo-lactone product **2.57** was treated with different nucleophiles such as 4-chlorobenzylamine and morpholine to obtain substituted products. The secondary amine **2.58** was derived from the S_N2 reaction with 4-chlorobenzylamine in 12%

isolated yield. Interestingly, the reaction with morpholine provided the tricyclic compound **2.59** instead of tetracyclic sultam **2.60** resulting from inherent basicity of the nucleophile (Scheme 2.18).

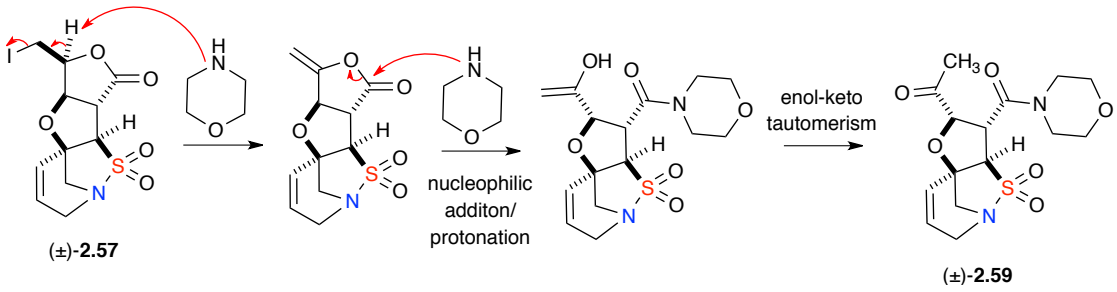


Figure 2.2

Iodo-compound **2.57** underwent elimination reaction with morpholine to provide an *exo* double bond containing γ-lactone intermediate. The compound **2.59** was derived from nucleophilic addition to carbonyl carbon followed by enol-keto tautomerization (Figure 2.2).

2.3 Conclusions

In conclusion, the generation of a small collection of several bi-, tri-, and tetracyclic sultams has been obtained in an overall DOS-based approach utilizing an ROM–RCM–CM cascade strategy. Several tricyclic sultams bearing various functional groups were derived from a diastereoselective IMDA reaction in good yields and selectivity as precursors for the metathesis cascade strategy. The ROM–RCM–CM proceeded in good to excellent yields, generating sultams possessing skeletally diverse that was controlled by elements incorporated into the sultam precursors or via the cross metathesis partner selected.

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(20) The 1:1 ratio of diastereomers was indistinguishable by ^{1}H. However, ^{13}C NMR spectroscopy was able to distinguish both as reported in Supplementary data.

(21) Diastereomeric ratio of 1.43:1.0 was determined by ^{1}H NMR analysis of crude 15.

(22) Previous results by both Hoffman and Howell have demonstrated higher selectivity with a series of serine-derived amino ketones: (a) Hoffman, R. V.; Tao, J. "A Synthesis of *D*-Erythro- and *L*-Threo-Sphingosine and Sphinganine Diastereomers via the Biomimetic Precursor 3-Ketosphinganine." *J. Org.*

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(26) Quantitatively it was found that after 2 h, a 3:1 ratio of 28/27 was observed. However, when the same NMR sample was analyzed after 4 and then 12 h, a mixture of 2:1 of 28/27 was observed as in the ^{1}H NMR.

Chapter 3

Vinyl Sulfonamides in Diversity-Oriented Synthesis:

Utilizing 5- and 6-Membered Sultam Synthons for Library Production

3.1 Introduction

3.1.1 Aza-Michael Reaction

The conjugate addition reaction is one of the most useful methods to form new C–X (X = C, N and O) bonds.[1] The synthetic versatility of this reaction depends mainly on a variety of nucleophiles, as well as acceptors. Usually α,β-unsaturated carbonyl compounds are known as acceptors, and the nucleophiles can be either carbon- or heteroatom-centered moieties. However, different types of activating groups such as nitro, sulfonate, sulfoxide and phosphate have also been used as acceptors. Among a broad range of nucleophiles and activated olefins that can be employed in diverse transformations, the conjugate addition of nitrogen nucleophiles, formally known as the aza-Michael reaction, has been extensively studied. The aza-Michael reaction represents one of the most powerful strategies for the C–N bond formation present in a variety of biologically active β-amino compounds or related derivatives.[2] As such, it has been widely used for the synthesis of natural products as well as nitrogen-containing heterocyclic small molecules.[3] Recently, several conjugate addition reactions have been applied to small library productions.[4] In particular, Schreiber and coworkers reported the diastereoselective intramolecular aza-Michael reaction to produce nitrogen-containing heterocyclic compounds using chiral, non-racemic substrates in a diversity-oriented synthesis (DOS) approach.[5]

Ring-closing metathesis (RCM) remains a widely used and powerful approach for the synthesis of complex molecules of various ring size. Our group has

previously utilized RCM for the generation of simple 5-, 6- and 7-membered sultam derivatives from the corresponding allyl and vinyl sulfonamides (Figure 3.1).[6] In addition to sultams, we have reported the utilization of RCM for the synthesis of *P*-heterocycles,[7] phosphonosugars,[8] and sulfamide peptidomimetics.[9]

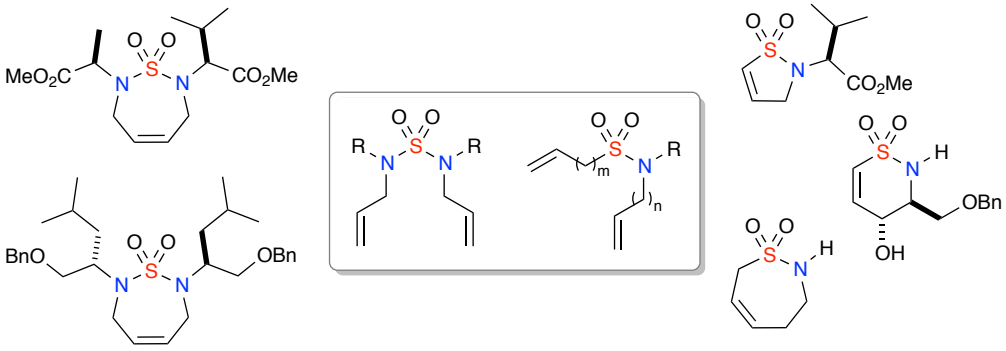


Figure 3.1 *RCM approaches to S-heterocycles.*

An inherent feature of using an RCM approach with vinyl sulfonamides to construct sultams, is that the corresponding sultam retains the α,β-unsaturated functionality incorporated within the generated cycle. The resulting α,β-unsaturated γ-sultam is an ideal synthon with several functional handles that can be applied to different types of reactions such as aza-Michael, cycloaddition and alkylation/arylation reactions to achieve diverse sultams (Figure 3.2). Our group has already reported the application of efficient oxa- and aza-Michael reaction protocols for the generation of sultams via intermolecular Michael cyclizations.[10] In the study discussed below, we investigate several reactions of α,β-unsaturated sultams to generate diverse sultam compounds.

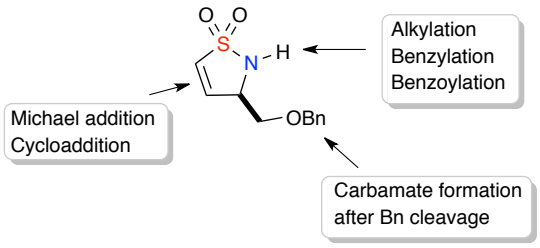
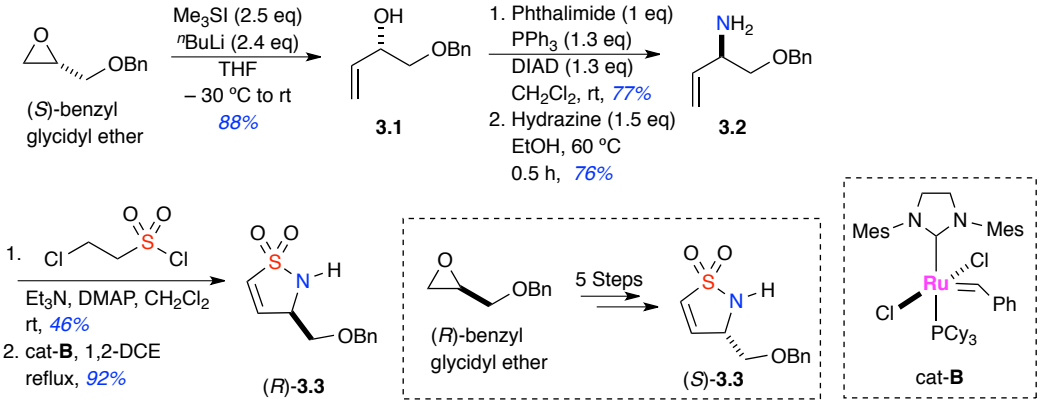


Figure 3.2 *Representative general strategy utilizing α,β-unsaturated sultam.*

3.2 Results and Discussion

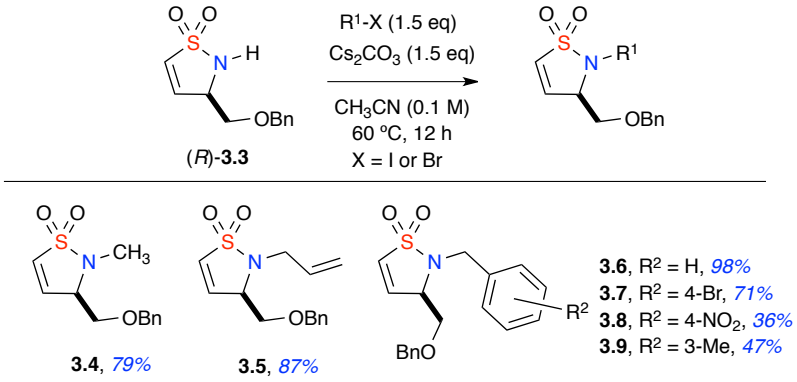
3.2.1 Diversifications of 2,3-Dihydroisothiazole 1,1-Dioxide Sultams

α,β-Unsaturated γ-sultam (*R*)-**3.3** was derived from commercially available starting material (*S*)-benzyl glycidyl ether in five steps (Scheme 3.1). The glycidyl ether underwent epoxide ring opening with trimethylsulfonium iodide in the presence of ^{n}BuLi at -30 ºC to provide allylic alcohol **3.1**. The resultant allylic alcohol was reacted under Gabriel primary amine synthesis conditions to yield allylamine derivative **3.2** in 2 steps.[6b] The primary amine **3.2** was coupled with 2-chloroethanesulfonyl chloride to afford corresponding vinyl sulfonamide in 46% isolated yield. The desired (*R*)-α,β-unsaturated γ-sultam product **3.3** was obtained in 92% isolated yield from the RCM reaction. In addition, with the same protocol, the enantiomer of sultam (*S*)-**3.3** was produced from (*R*)-benzyl glycidyl ether (Scheme 3.1).



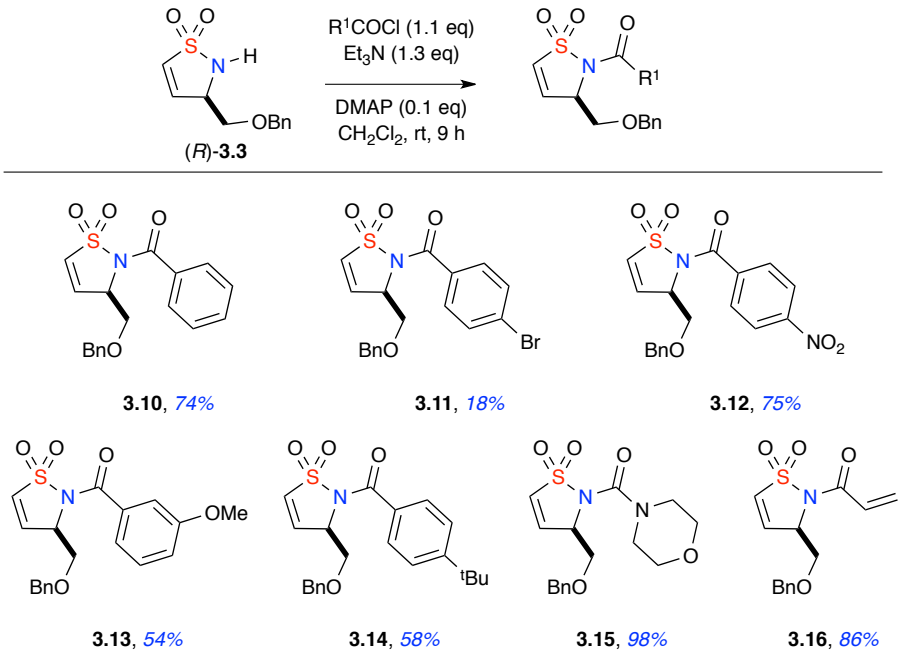
Scheme 3.1

Having successfully synthesized sultam **3.3**, the first position manipulated for diversification was the nitrogen atom of sultam **3.3**. Simple alkylation was applied to generate tertiary sultams. Sultam **3.3** was reacted with an alkyl halide, including methyl iodide and allyl bromide, in the presence of Cs_2CO_3 in CH_3CN at 60 ºC, to furnish **3.4** and **3.5** in 79% and 87% isolated yields, respectively (Scheme 3.2). Utilizing the similar reaction conditions, sultams **3.6**–**3.9** were derived from various substituted benzyl halides in 36–98% yields.



Scheme 3.2

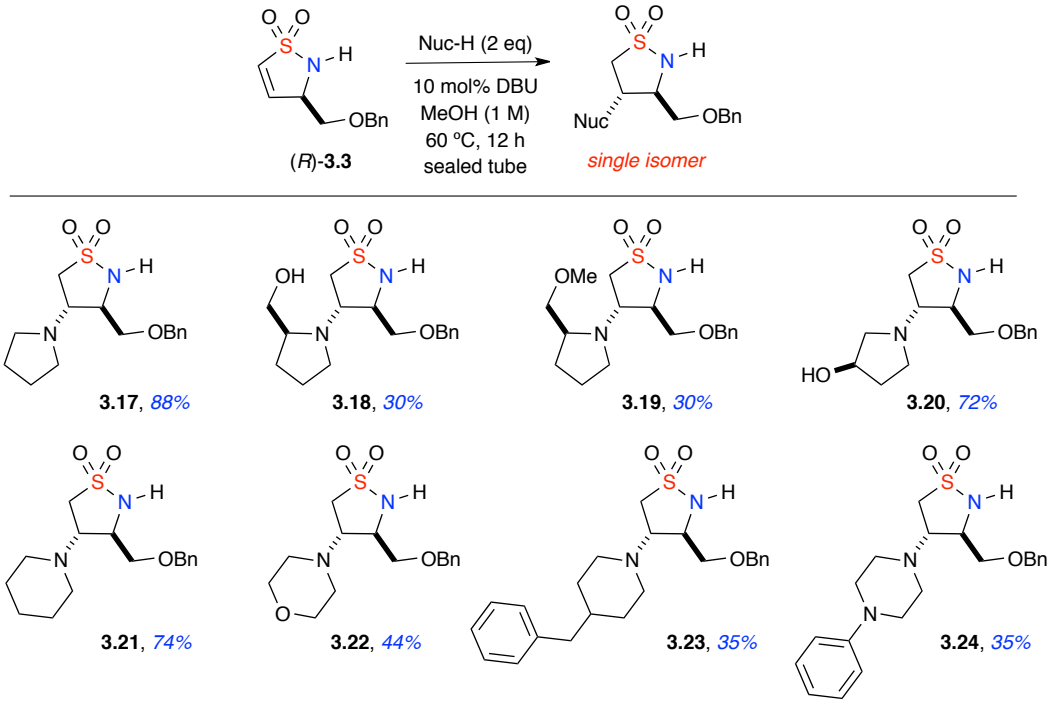
Sultam **3.3** was next subjected to acylation reactions with acyl chloride (1.1 eq), Et_3N (1.3 eq) in the presence of DMAP in CH_2Cl_2 at room temperature to afford desired products **3.10**–**3.16** in 18–98% yields. In particular, the reactions with 4-morpholinecarbonyl chloride as well as acryloyl chloride provided the corresponding products with good yields (98% and 86%, respectively) (Scheme 3.3).



Scheme 3.3

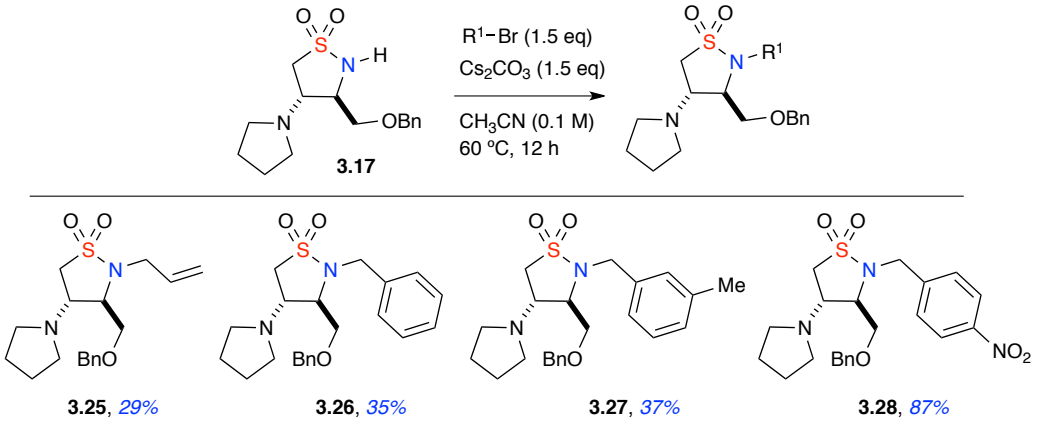
These studies were further extended with the application of the aza-Michael reaction onto sultam **3.3** to obtain a series of saturated 5-membered sultams. In this method, only secondary cyclic amines were used as nucleophiles for the aza-Michael reaction since the purification with primary amines was problematic. We are currently working to rectify this problem. Therefore, we began the reaction with sultam **3.3** being subjected to the aza-Michael reaction with 2 equivalents of pyrrolidine in the presence of DBU (10 mol%) in MeOH at 60 ºC. After 12 hours, the

reaction furnished the desired product **3.17** in 88% yield after purification. Both 5- and 6-membered secondary cyclic amines underwent aza-Michael reaction with moderate yields, and the reaction provided a single isomer of product for each reaction due to the C3-stereogenic center of sultam **3.3** (Scheme 3.4).



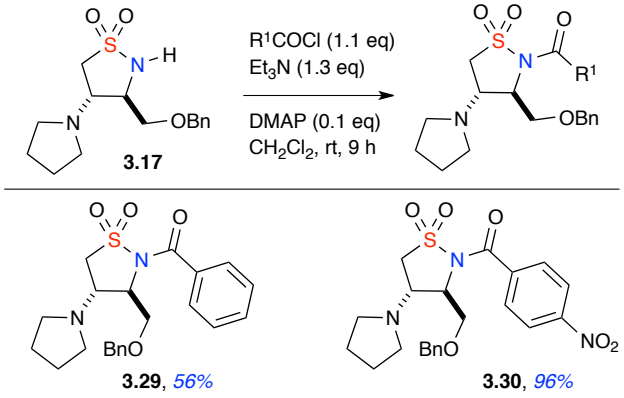
Scheme 3.4

In addition to these results, sultam **3.17** derived from the aza-Michael reaction was further diversified via alkylation of the sultam nitrogen (Scheme 3.5). *N*-Allyl sultam **3.25** was derived from the reaction with allyl bromide in the presence of Cs_2CO_3 in CH_3CN at 60 ºC with 29% yield. Benzyl derivatives **3.26–3.28** were obtained under the same reaction condition with 35–87% isolated yields.



Scheme 3.5

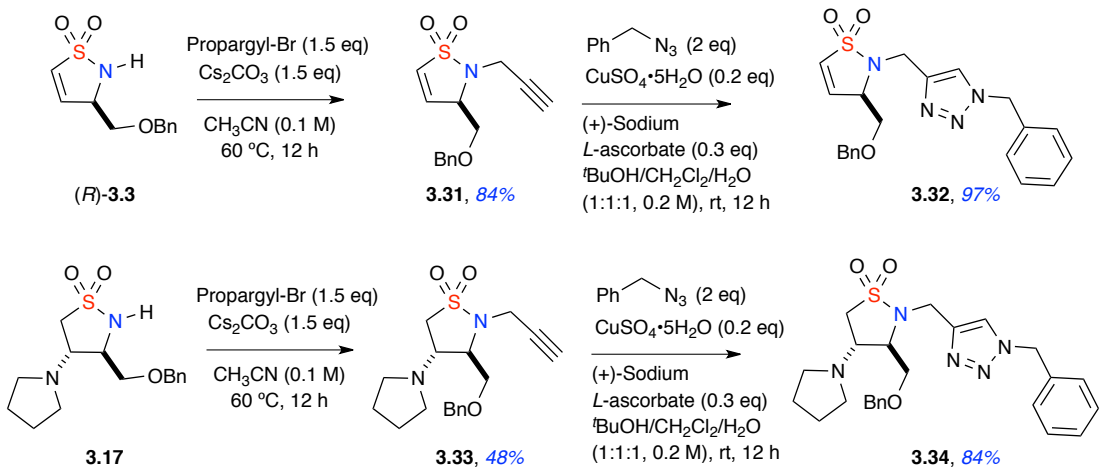
The free N–H of sultam **3.17** also underwent the acylation reaction with acyl chlorides, including benzoyl chloride and 4-nitrobenzoyl chloride, to afford the corresponding sultams (**3.29** and **3.30**) in 56% and 96% yields, respectively (Scheme 3.6).



Scheme 3.6

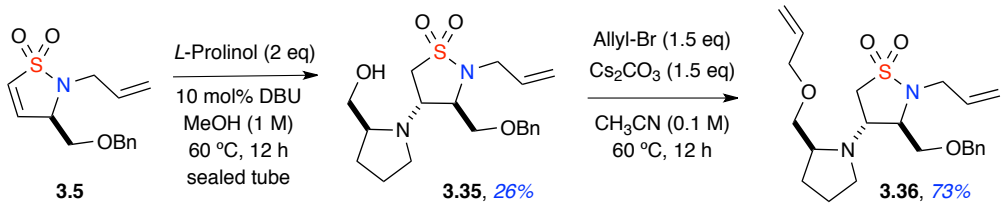
In addition to these earlier results, another application was developed utilizing *γ*-sultams **3.3** and **3.17** (Scheme 3.7). The sultams were subjected to the propargylation under standard alkylation reaction conditions. The alkynyl group underwent subsequent [3+2]-cycloaddition reactions with benzyl azide to afford

1,2,3-triazole compounds **3.32** and **3.34** in good isolated yields.



Scheme 3.7

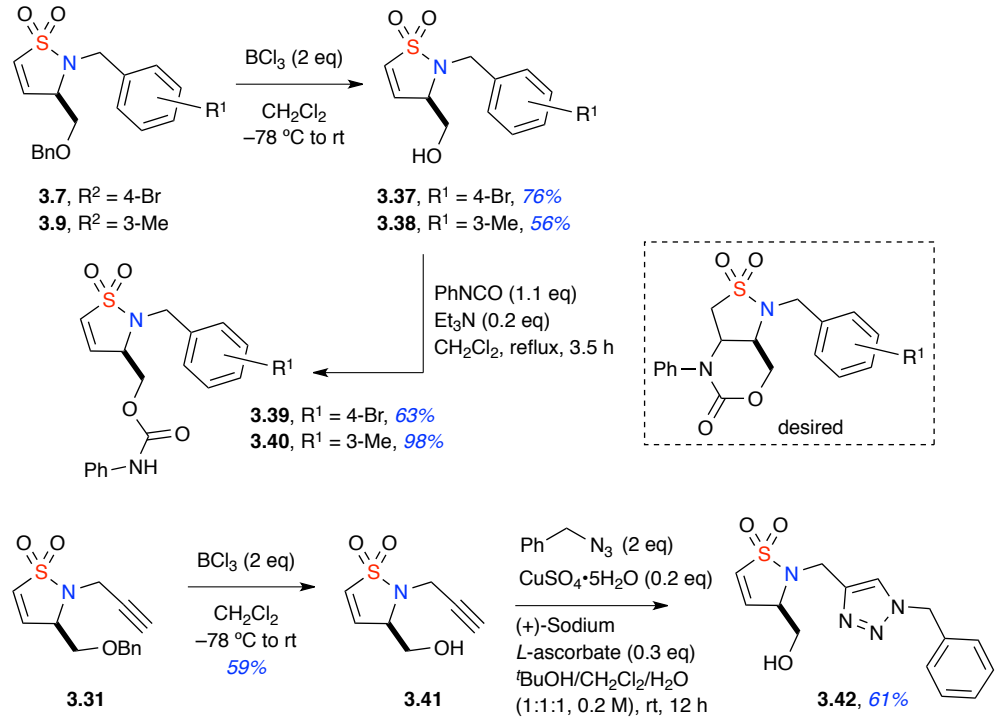
Additionally, *N*-allylated α,β-unsaturated γ-sultam **3.5** was also subjected to the aza-Michael reaction with *L*-prolinol under standard reaction conditions, to generate the corresponding sultam **3.35** in 26% yield. Because sultam **3.35** possesses a free alcohol, the allylation reaction was carried out to afford sultam **3.36** in 73% isolated yield (Scheme 3.8).



Scheme 3.8

Removal of the benzyl group provided a primary alcohol. However, the product with free N–H could not be recovered from the reaction due to the compound's increased solubility in water, we are currently trying to circumvent this problem. Therefore, the benzylated or alkylated products were also used for this

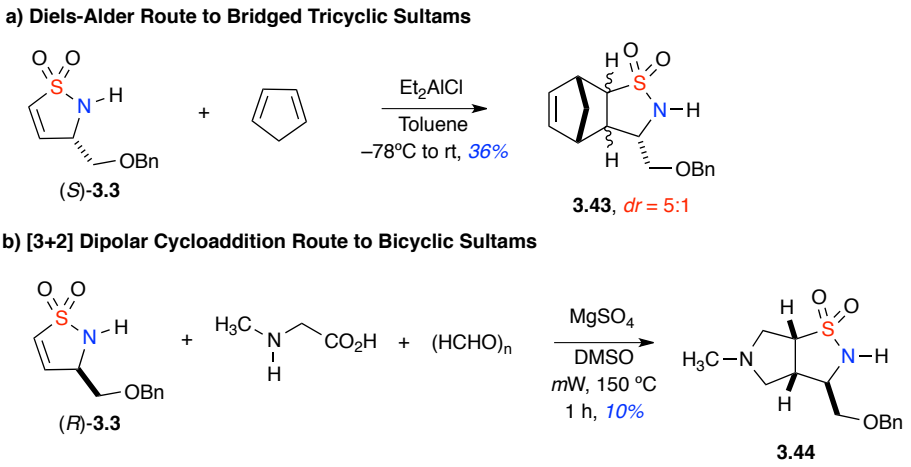
strategy. Benzylated sultams **3.7** and **3.9** were treated with 2 equivalents of BCl_3 at -78 ºC to obtain the primary alcohol-containing products **3.37** and **3.38** in moderate yields. The reaction between an alcohol and phenyl isocyanate to obtain cyclized product was previously reported.[6b] Based on this precedence each alcohol compound was subjected to reaction with phenyl isocyanate (1.1 eq) in the presence of Et_3N (0.2 eq) in CH_2Cl_2. After 3.5 hours, none of the desired cyclized products were obtained; instead the corresponding uncyclized carbamate products **3.39** and **3.40** were isolated with good yields. The propargylated sultam **3.31** was also treated with BCl_3 to obtain



Scheme 3.9

primary alcohol **3.41** in 59% yield. After [3+2]-cycloaddition with benzyl azide, sultam **3.42** containing a triazole moiety as well as a primary alcohol, was obtained in 61% yield (Scheme 3.9).

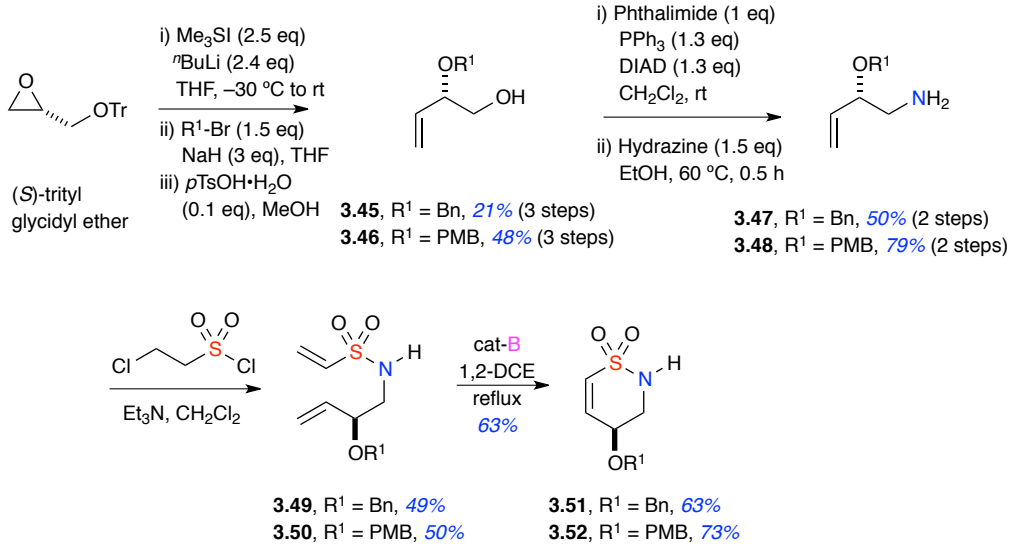
Building upon these results, we next investigated the cyclization reaction including Diels-Alder and 1,3-dipolar cycloaddition with α,β-unsaturated γ-sultam to produce bi- and tricyclic sultams. The Diels-Alder reaction provided bridged tricyclic sultams, while the 1,3-dipolar cycloaddition reaction furnished bicyclic sultams (Scheme 3.10).[11] The cyclization began with cyclopentadiene (7 eq) in the presence of Et_2AlCl (2 eq) in toluene at -78 ºC to yield bridged tricyclic sultam **3.43** in 36% yield (Scheme 3.10a). Bicyclic sultam **3.44** was derived from cycloaddition reaction of sultam **3.3** with sarcosine (5 eq) and paraformaldehyde (12 eq) in the presence of $MgSO_4$ in DMSO under microwave conditions with low yield.



Scheme 3.10

3.2.2 Diversification of 3,4-Dihydro-2*H*-1,2-thiazine 1,1-Dioxide Sultams

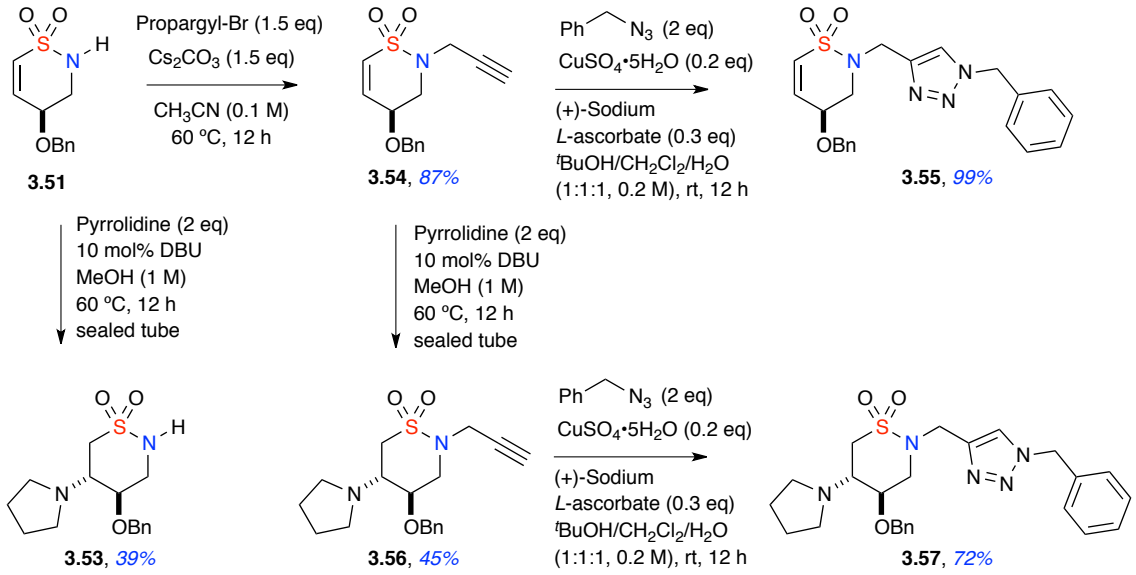
During this investigation, α,β-unsaturated δ-sultams **3.51** and **3.52** were also prepared. (*S*)-Trityl glycidyl ether underwent the epoxide ring opening reaction with trimethylsulfonium iodide (2.5 eq) in the presence of ^{n}BuLi (2.5 eq) at -30 ºC to provide the corresponding allylic alcohol. The secondary alcohol was protected with either benzyl or *p*-methoxybenzyl group followed by deprotection of trityl group in the presence of *p*TsOH•H_2O in methanol, to produce the primary alcohol **3.45** and **3.46** in 21% and 48% yields, respectively. The primary amine resulting from Gabriel amine synthesis was coupled with 2-chloroethanesulfonyl chloride under standard condition to generate vinyl sulfonamides **3.49** and **3.50** in moderate yields. RCM in the presence of cat-**B** provided desired δ-sultams **3.51** and **3.52** in 63% and 73% yield, respectively (Scheme 3.11).



Scheme 3.11

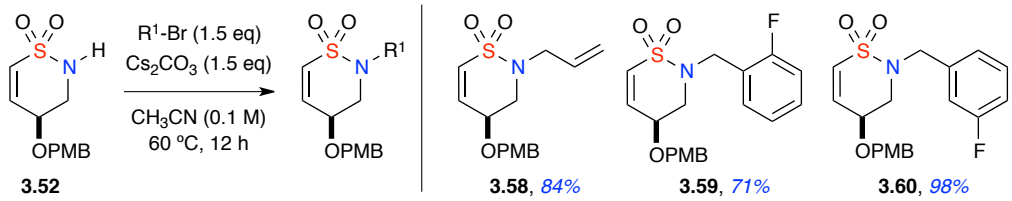
With these scaffolds in hand, the aza-Michael reaction was applied under

standard reaction conditions, to furnish sultam **3.53**. After propargylation, the alkynyl group underwent a simple [3+2]-cycloaddition reaction with benzyl azide to produce α,β-unsaturated δ-sultam **3.55** in 99% yield. On the other hand, the δ-sultam **3.54** was reacted with pyrrolidine followed by [3+2]-cycloaddition reaction under standard reaction conditions, to afford the final compound **3.57** in 72% isolated yield (Scheme 3.12).



Scheme 3.12

Furthermore, the α,β-unsaturated δ-sultam **3.52** was also subjected to alkylation and benzylation reactions. Allyl bromide, 2-fluoro and 3-fluorobenzyl bromides were used as coupling partners to afford the corresponding sultams (**3.58**–**3.60**) in good yields (Scheme 3.13).



Scheme 3.13

3.2.3 141-Member Library Production

Based on the aforementioned aza-Michael reactions, we were able to produce a library of isothiazolidine 1,1-dioxides utilizing an RCM-aza-Michael protocol.

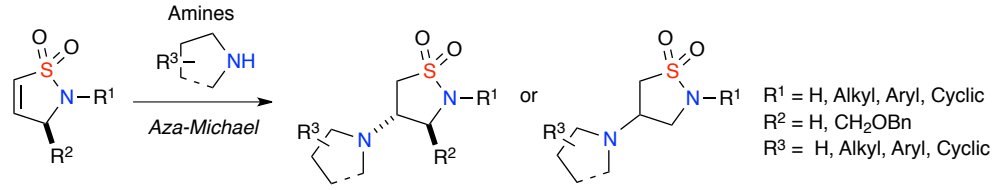
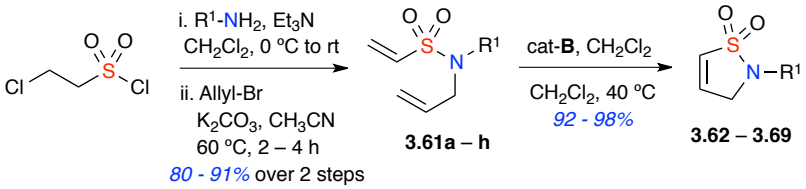


Figure 3.3 *Proposed diversification of core RCM-derived dihydroisothiazole 1,1-dioxide scaffolds via intermolecular aza-Michael reaction.*

The ten core scaffolds of dihydroisothiazole 1,1-dioxides were synthesized from commercially available 2-chloroethane sulfonyl chloride (Table 3.1). Key RCM precursors **3.61a**–**h** were generated via a 2-step procedure where a variety of amines were sulfonylated followed by allylation to generate vinyl sulfonamides **3.61a**–**h** in good yield and on multi-gram scale. Cyclization of the precursors **3.61a**–**h** via RCM utilizing metathesis catalyst [cat-**B**],[12,13] was successfully achieved yielding the desired cyclized dihydroisothiazole 1,1-dioxide derivatives **3.62**–**3.69** in excellent yields. In addition to dihydroisothiazole 1,1-dioxide scaffolds **3.62**–**3.69**, two

derivatives (*R*)-**3.3** and (*S*)-**3.3** possessing a chiral center alpha to the Michael acceptor were also used.

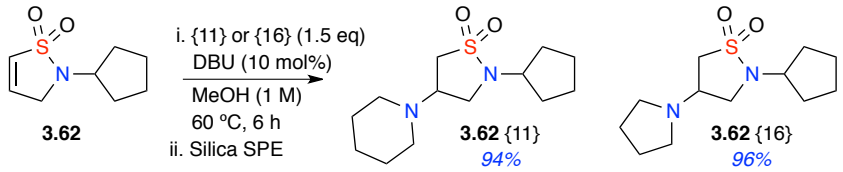
Table 3.1 *Synthesis of dihydroisothiazole 1,1-dioxide scaffolds **3.62–3.69** via an RCM protocol.*



Entry	R^1	Product	Yield
1	cyclopentyl	**3.62**	93 %
2	^{n}Bu	**3.63**	98 %
3	Bn	**3.64**	96 %
4	4-F-Bn	**3.65**	95 %
5	4-NO_2-Bn	**3.66**	98 %
6	$(CH_2)_2$Ph	**3.67**	96 %
7	4-Me-Bn	**3.68**	93 %
8	cyclohexyl	**3.69**	92 %

With these scaffolds readily synthesized on gram-scale, the diversification of the dihydroisothiazole 1,1-dioxide cores was investigated. Utilizing previously reported conditions developed within our group for intermolecular oxa- and aza-Michael cyclizations,[10] the diversification of **3.62** via an intermolecular aza-Michael with piperidine {11} and pyrrolidine {16} was investigated (Scheme 3.14). This study initially focused on the screening of a range of conditions varying amine equivalents (1–2 eq), base equivalents (DBU), solvent (MeOH, THF, EtOAc and

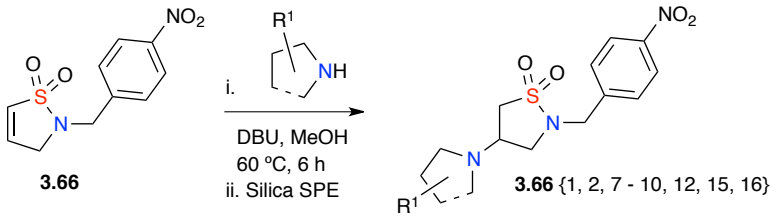
DMF), concentration (0.5–2 M), temperature (rt–100 ºC), and heating platforms (thermal vs. microwave).



Scheme 3.14 *Optimization of aza-Michael conditions with amines {11} and {16} utilizing scaffold **3.62**.*

A prototype library was investigated for the diversification of dihydroisothiazole 1,1-dioxide **3.66** with a variety of secondary amine nucleophiles under the optimized condition (Table 3.2). Reactions were carried out in 1 dram vials on reaction blocks, whereby crude reaction mixtures were diluted in EtOAc, filtered through a silica SPE to remove excess amine and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). The prototype library successfully generated all the desired products in good yield and excellent final purity after automated preparative reverse phase HPLC, with good crude purities (71–99%) and crude masses after filtration via silica SPE to remove excess amines.

Table 3.2 *Prototype library utilizing dihydroisothiazole 1,1-dioxide **3.66**.*



Entry	Product	Crude purity	Yield	Final purity
1	**3.66** {1}	94%	40%	100%
2	**3.66** {2}	89%	45%	100%
3	**3.66** {7}	89%	52%	100%
4	**3.66** {8}	71%	40%	96%
5	**3.66** {9}	84%	51%	96%
6	**3.66** {10}	91%	46%	99%
7	**3.66** {12}	99%	50%	100%
8	**3.66** {15}	83%	33%	96%
9	**3.66** {16}	93%	48%	100%

[a]Reaction conditions: Dihydroisothiazole 1,1-dioxide **3.66** (75 mg, 1 eq.), amine (1.5 eq), DBU (10 mol%), dry MeOH (1 M), 60 ºC, 6h. [b]Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c]Purity was determined by HPLC with peak area (UV) at 214 nm and % rounded up to nearest 1%.

With the successful synthesis of the 9-member prototype library, two libraries **A** and **B** were proposed for the synthesis of 144-isothiazolidine 1,1-dioxide derivatives utilizing scaffolds (*R*)- and (*S*)-**3.3**, as well as **3.62**–**3.69** and two sets of secondary amines (**A** and **B** in Figure 3.4).

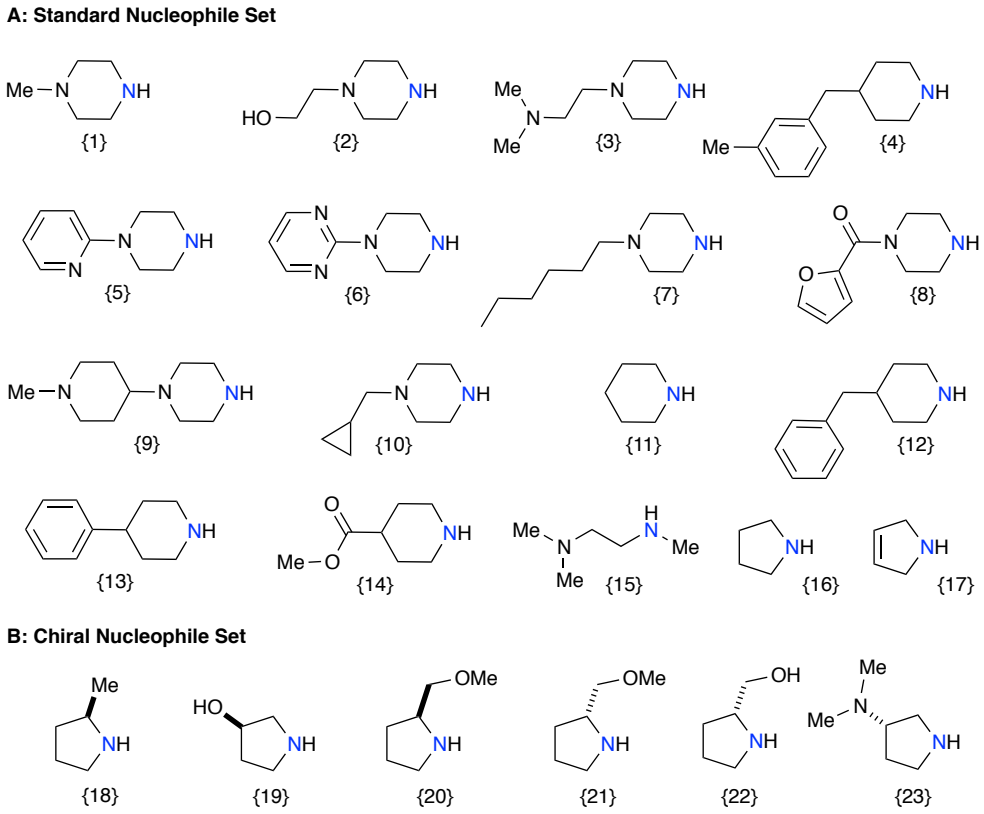
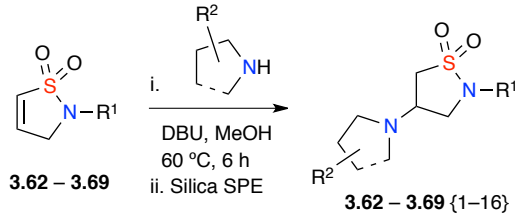
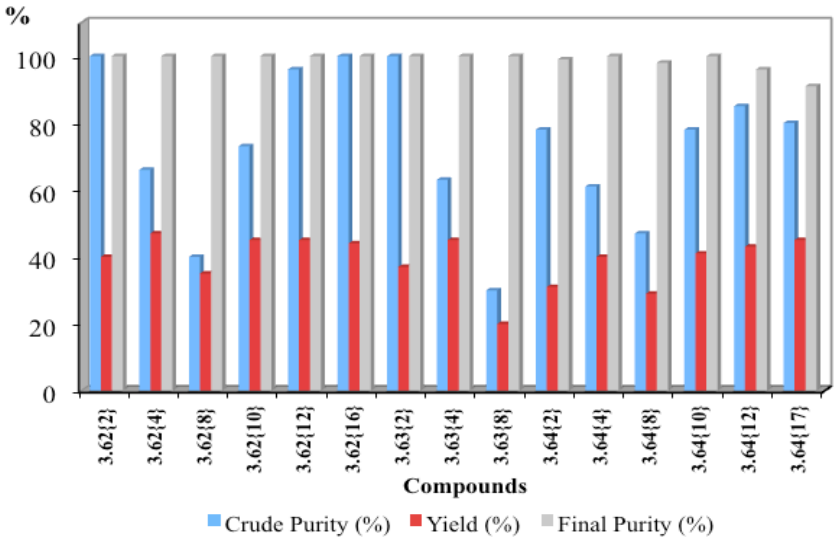


Figure 3.4 *Set of secondary amine nucleophiles for library synthesis.*

Utilizing the optimized conditions, library **A** (116-member) was generated utilizing scaffolds **3.62**–**3.69** and amine set **A**, followed by QC and purification using automated preparative reverse phase HPLC (detected by mass spectroscopy). A total of 113 out of 116 compounds were prepared,[14] with good overall yield and mass recovery with all compounds with final purity >90% after automated purification (Graph 3.1).[15]

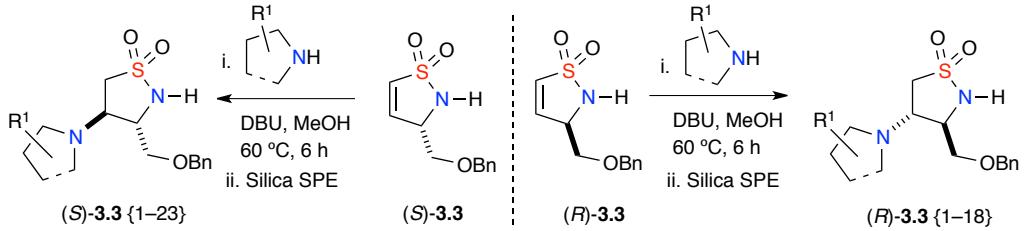
Graph 3.1 *Library A: aza-Michael of scaffolds **3.62–3.69**.*

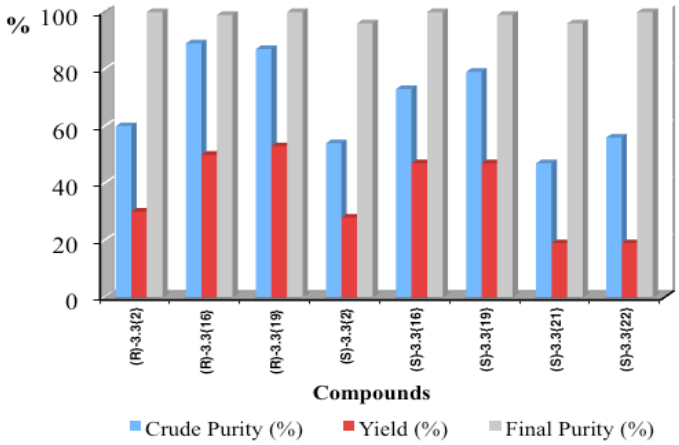




Upon completion of library **A** (116-member), library **B** (28-member) was generated utilizing scaffolds (*R*)-**3.3** and (*S*)-**3.3** with both amine set **A** and amine set **B**, followed by QC and purification using automated preparative reverse phase HPLC (detected by mass spectroscopy). A total of 28 out of 28 compounds were prepared, with good overall yield with all compounds with final purity >90% after automated purification (Graph 3.2)

Graph 3.2 *Library B: aza-Michael of scaffolds (R)-**3.3** and (S)-**3.3**.*





3.3 Conclusions

In conclusion, we have reported several reaction pathways to generate diverse sultam compounds using α,β-unsaturated sultams generated from RCM. Utilizing aza-Michael reaction, we have developed an efficient protocol for synthesis of a 141-member collection of isothiazolidine 1,1-dioxide derivatives. Utilizing RCM of vinyl sulfonamides, ten dihydroisothiazole 1,1-dioxide core scaffolds were generated on gram-scale followed by efficient diversification utilizing an aza-Michael protocol with a variety of secondary amines. A 144-member was undertaken with 141/144 successfully yielding the desired products after automated preparative reverse phase HPLC (detected by mass spectroscopy), giving a 97.9% pass rate. These compounds

have been submitted to a number of biological collaborators within the NIH Molecular Libraries Probe Center Network (MLPCN) for evaluation of their biological activity in high-throughput screening.

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(13) A variety of metathesis catalyst were investigated, including [$(PCy_3)_2(Cl)_2Ru$=CHPh; cat-**A**], [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh; cat-**B**], and the Hoveyda-Grubbs 2nd-generation catalyst. In all cases studied, cat-**B** was ideal in both thermal stability and initiation rate.

(14) 3 Samples from were lost during automated preparative reverse phase HPLC.

(15) Representative compounds with full data set available in supplementary information.

Chapter 4

Intramolecular C-Arylation to Tricyclic, Biaryl Sultams:

Long-range Asymmetric Induction in an Atropdiastereoselective,

Thermodynamic Equilibration Process

4.1 Introduction

4.1.1 Biaryl, Axially Chiral Compounds and Atropselectivity

Biaryl small molecules displaying axial chirality have surfaced as key scaffolds in early phase drug discovery.[1] The presence of axial chirality in biaryl systems is the consequence of hindered rotation around the biaryl bond when *ortho* substituents are present in both ring systems. Recently, LaPlante and coworkers addressed the importance of atropisomers and provided a practical computational guideline for them in drug discovery and development that is dependent on rotation energy barriers and interconversion half-lives.[1] A number of prominent examples have emerged in recent years, including: acyclic biaryl compounds such as quinoxalinedione (**4.1**, Figure 4.1), korupensamine A (**4.2**), BMS-207940 (**4.3**),

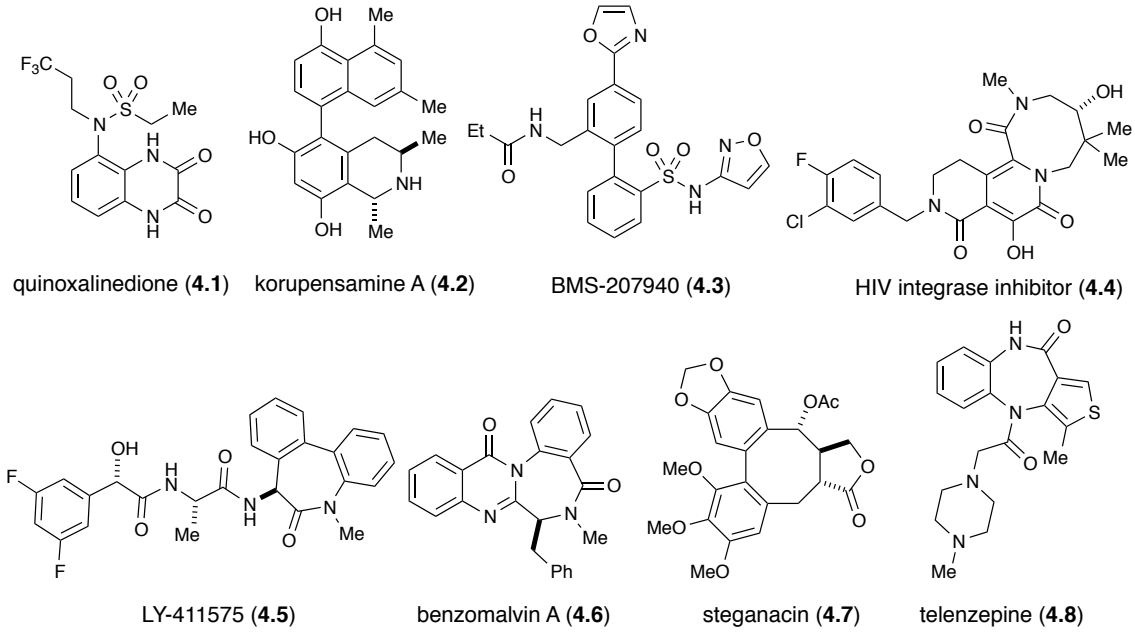
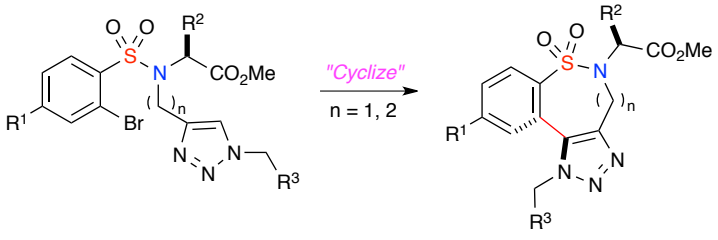


Figure 4.1 *Representative bioactive axially chiral compounds.*

the cyclic biaryl compounds HIV integrase inhibitor (**4.4**), LY-411575 (**4.5**), benzomalvin (**4.6**), steganacin (**4.7**), and telenzepine (**4.8**).[2] In response to this impressive biological activity, a number of elegant methods have been reported for atropselective synthesis of axially chiral biaryl compounds. In general, three strategies have been utilized in the field to produce atropisomeric biaryl compounds: (i) resolution of stereochemically undefined (racemic/diastereomeric) biaryls,[3] (ii) direct asymmetric biaryl coupling,[4] and (iii) atropselective biaryl synthesis by construction of the second aromatic ring.[5]

We now report a remarkable intramolecular *C*-arylation process of the triazole-containing tertiary sulfonamide **4.9a** (Scheme 4.1) leading to a novel class of tricyclic, biaryl sultam **4.9b** possessing benzothiazepine (n = 1)/benzothiazocine (n = 2) 1,1-dioxides and triazole subunits. These unique structures were designed with hopes of bringing the synergies between bioactive benzothiazepine/benzothiazocine 1,1-dioxides, 1,2,3-triazoles, and biaryl compounds which all have received much attention over the past decade and found wide application in medicinal chemistry because of their unique chemical and structural properties.



4.9a **4.9b**

Scheme 4.1

1,4-Benzodiazepines fused to five-membered heterocycles are well-known drugs for the treatment of central nervous system (CNS) disorders.[6] Alprazolam (**4.10**) is common anxiolytic agent,[7] flumazenil (**4.11**) belongs to the family of cognition enhancers,[8] while G-7453 (**4.12**) has been reported as a potential fibrinogen antagonist.[9]

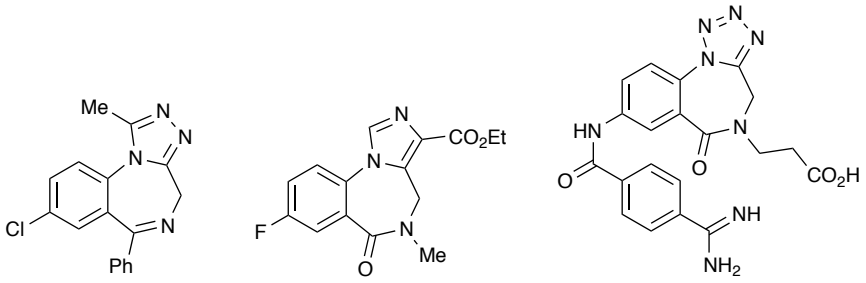
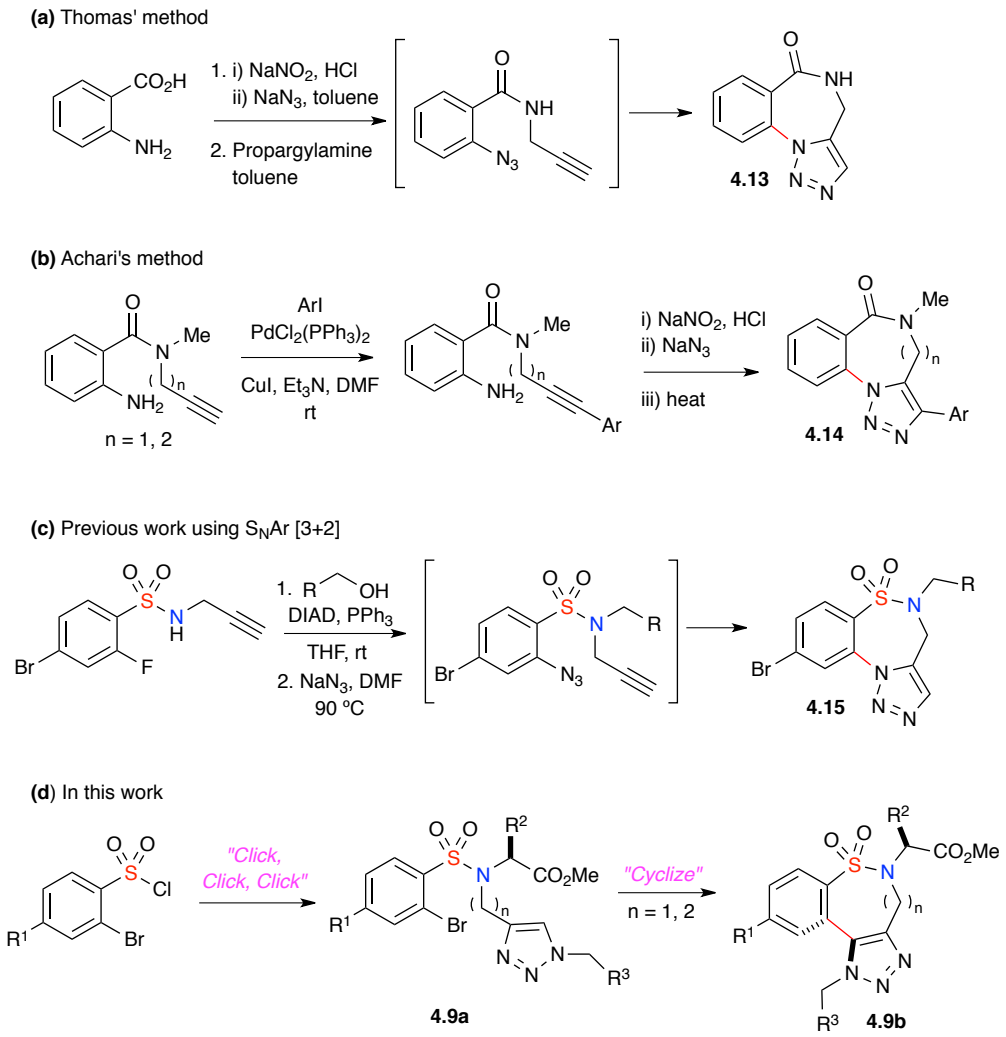


Figure 4.2 *Representative 1,4-benzodiazepine compounds.*

1,2,3-Triazole compounds exhibited various biological activities including anti-HIV activity[10,11] and antimicrobial activity against Gram-positive bacteria.[12] The cycloaddition reaction between azides and alkynes is one of the most widely used approaches to 1,2,3-triazoles. More specifically, the Huisgen's 1,3-dipolar [3+2]-cycloaddition of azide and alkynes is undoubtedly the most widely used method to synthesize 1,2,3-triazoles, whereby Cu(I)-catalyst,[13] and Ru(II)-catalyst[14] can now be utilized to regioselective generate 1,4- or 1,5-disubstituted triazoles, respectively. A unique class of triazole-containing benzodiazepines were produced by Thomas who reported a one-pot alkyne-azide cycloaddition reaction starting from readily available anthranilic acids to derive **4.13** in an overall C–N bond forming process [Scheme 4.2 (a)].[9] In addition, Achari and coworkers reported one-pot reactions involving

diazotization/azidation followed by cycloaddition reaction to afford the unique triazole-containing benzodiazepine compounds **4.14** [Scheme 4.2 (b)].[15] Previously we reported the generation of a triazole-containing sultam using S_NAr, followed by a [3+2]-cycloaddition between the alkyne and azide, to construct the tricyclic, biaryl sultam **4.15** [Scheme 4.2 (c)].[16]



Scheme 4.2 *(a) and (b) Representative examples for preparation of benzodiazepines. (c) Generation of thiadiazepine 6,6-dioxide. (d) General strategy in this work.*

C-Arylation is a well-known alternative method for functionalization of 1,2,3-triazole compounds. In 2007, Gevorgyan and coworkers reported a method to synthesize multi-substituted 1,2,3-triazoles via Pd-catalyzed C-5 arylation between 1,2,3-triazoles and aryl bromides in an overall C–C bond forming process.[17] In contrast, Potukuchi and coworker showed examples using Pd-catalyzed intramolecular oxidative arylation for synthesis of hetero-annulated triazoles using a C–C bond forming process.[18]

The work presented herein utilizes *C*-arylation of a substituted triazole as a strategy to generate a novel class of tricyclic, biaryl sultams [Scheme 4.2 (d)]. In the course of X-ray crystallographic analysis of product sultams within a series of analogs, as well as detailed NMR studies, *vide infra*, we have uncovered a number of notable and interesting structural features in both solid and solution phases that will be described throughout the chapter. Namely, in the amino ester-derived sultams, remote 1,5- and 1,6-asymmetric induction emanating from the external stereogenic center is operative, whereby a favorable Cα–H/S=O *syn* pentane interaction, is

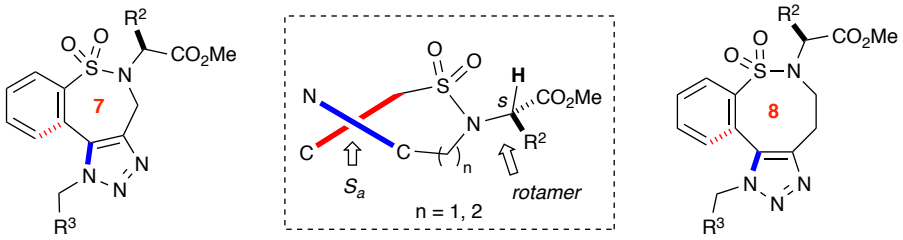


Figure 4.3

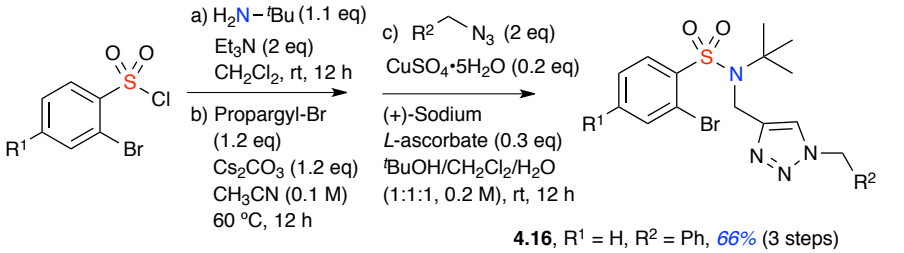
believed to be the source of asymmetric induction for a highly atropdiastereoselective thermodynamic equilibration process yielding a low energy conformer of "like"

configuration (S,S_a). This chapter will initially describe the synthesis of all analogs before discussing the X-ray and NMR studies that have led to these conclusions.

4.2 Result and Discussion

4.2.1 Synthesis of 7-Membered Tricyclic, Biaryl Sultams Derived from *tert*-Butylamine

Initial investigations focused on the generation of the 7-membered benzofused tricyclic, biaryl sultam using a simple alkylamine starting material. For each reaction, two different 2-bromobenzenesulfonyl chlorides, as well as three azides [benzyl azide, 4-methylbenzyl azide and cyclohexylmethyl azide], were employed to generate the desired triazole-containing benzenesulfonamides. Commercially available 2-bromobenzenesulfonyl chloride was coupled with *tert*-butylamine under standard conditions (Et_3N and CH_2Cl_2 at rt) to provide the corresponding secondary benzenesulfonamides.



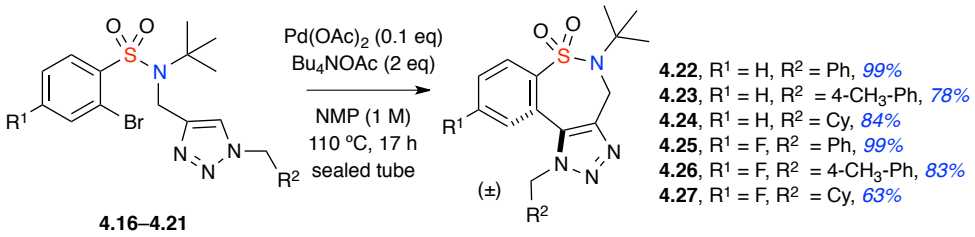
4.16, R^1 = H, R^2 = Ph, *66%* (3 steps)
4.17, R^1 = H, R^2 = 4-CH_3-Ph, *68%* (3 steps)
4.18, R^1 = H, R^2 = Cy, *71%* (3 steps)
4.19, R^1 = F, R^2 = Ph, *77%* (3 steps)
4.20, R^1 = F, R^2 = 4-CH_3-Ph, *87%* (3 steps)
4.21, R^1 = F, R^2 = Cy, *83%* (3 steps)

Scheme 4.3

After propargylation (propargyl bromide, Cs_2CO_3 in CH_3CN at 60 ºC), the generated tertiary benzenesulfonamide was subjected to Huisgen [3+2]-cycloaddition

reaction in the presence of $CuSO_4$•$5H_2O$ (0.2 eq) and (+)-sodium *L*-ascorbate (0.3 eq) in $^tBuOH/CH_2Cl_2/H_2O$ (1:1:1, 0.2 M) at rt. Under these reaction conditions, a single regioisomer of **4.16–4.18** was obtained in good yields (66–71%). Using the same pathway, 2-bromo-4-fluorobenzenesulfonyl chloride was also converted to tertiary benzenesulfonamides **4.19–4.21** in good yields (77–87% overall yields for 3 steps, Scheme 4.3).

With triazole-containing, tertiary sulfonamides **4.16–4.21** in hand, *C*-arylation was carried out using catalytic $Pd(OAc)_2$ (10 mol%) and Bu_4NOAc (2 eq) as a base, in *N*-methylpyrrolidone (NMP) (0.5 M) at 110 ºC for 17 hours, to furnish the corresponding 7-membered sultams (Scheme 4.4). *C*-Arylation of benzenesulfonamides **4.16–4.18** provided 7-membered tricyclic, biaryl sultam compounds **4.22–4.24** in 78–99% isolated yields. 4-Fluoro-substituted, benzofused 7-membered sultams **4.25–4.27** were produced from benzenesulfonamide precursors **4.19–4.21**. The exchange of catalytic $Pd(OAc)_2$ with $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ also provided similar isolated yields.

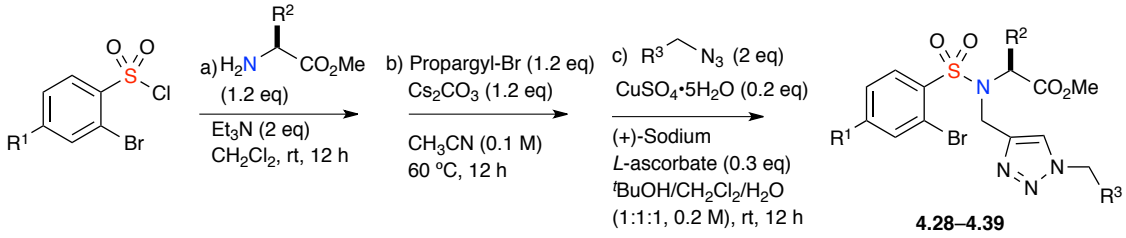


Scheme 4.4

4.2.2 Synthesis of 7-Membered Tricyclic, Biaryl Sultams Derived from Chiral, Non-racemic Amino Esters

The effect of an amino ester-derived external chiral center on the *C*-arylation process was next investigated. Using the same reaction sequence, a series of 2-bromobenzenesulfonamides were produced using *L*-valine methyl ester hydrochloride, as well as *L*-leucine methyl ester hydrochloride.

Table 4.1



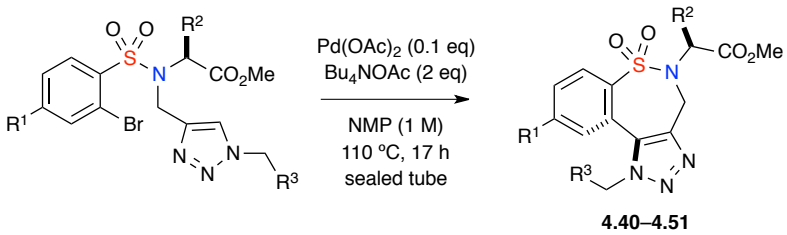
4.28–4.39

Entry	R^1	R^2	R^3	Product	Yield
1	H	^{i}Pr	Ph	**4.28**	99%
2	H	^{i}Pr	4-CH_3-Ph	**4.29**	99%
3	H	^{i}Pr	Cy	**4.30**	72%
4	H	^{i}Bu	Ph	**4.31**	85%
5	H	^{i}Bu	4-CH_3-Ph	**4.32**	85%
6	H	^{i}Bu	Cy	**4.33**	69%
7	F	^{i}Pr	Ph	**4.34**	99%
8	F	^{i}Pr	4-CH_3-Ph	**4.35**	77%
9	F	^{i}Pr	Cy	**4.36**	70%
10	F	^{i}Bu	Ph	**4.37**	94%
11	F	^{i}Bu	4-CH_3-Ph	**4.38**	97%
12	F	^{i}Bu	Cy	**4.39**	98%

2-Bromobenzenesulfonyl chloride was coupled with *L*-valine methyl ester hydrochloride, followed by propargylation and [3+2]-cycloaddition reaction, under standard reaction conditions, to obtain the desired tertiary benzenesulfonamides **4.28**–**4.33** in good isolated yields (69–99%). 2-Bromo-4-fluorobenzenesulfonyl chloride was also converted to the corresponding secondary benzenesulfonamides and then treated with propargyl bromide. After Huisgen [3+2]-cycloaddition reaction with three azides, the reactions furnished the tertiary 2-bromobenzenesulfonamides (**4.34**–**4.39**) (Entries 7–12, Table 4.1).

Each benzenesulfonamide was subjected to the *C*-arylation reaction in the presence of $Pd(OAc)_2$. The results are summarized in Table 4.2. Both triazole containing valine ($R^2 = {}^{i}Pr$) and leucine ($R^2 = {}^{i}Bu$) methyl ester benzenesulfonamide analogues underwent *C*-arylation reaction with $Pd(OAc)_2$ and Bu_4NOAc in NMP at 110 ºC to furnish 7-membered tricyclic sultams **4.40**–**4.45** with moderate to good yields (Entries 1–6, Table 4.2). 2-Bromo-4-fluorobenzenesulfonamides (**4.46**–**4.51**) were converted to the corresponding tricyclic sultams under the Pd-catalyzed *C*-arylation reaction conditions in 25–86% yields (Entries 7–12, Table 4.2). Surprisingly, the glycine ethyl ester derivative did not undergo *C*-arylation and the *L*-alanine methyl ester analogues did not reach completion under the same reaction conditions described above.

Table 4.2



4.40–4.51

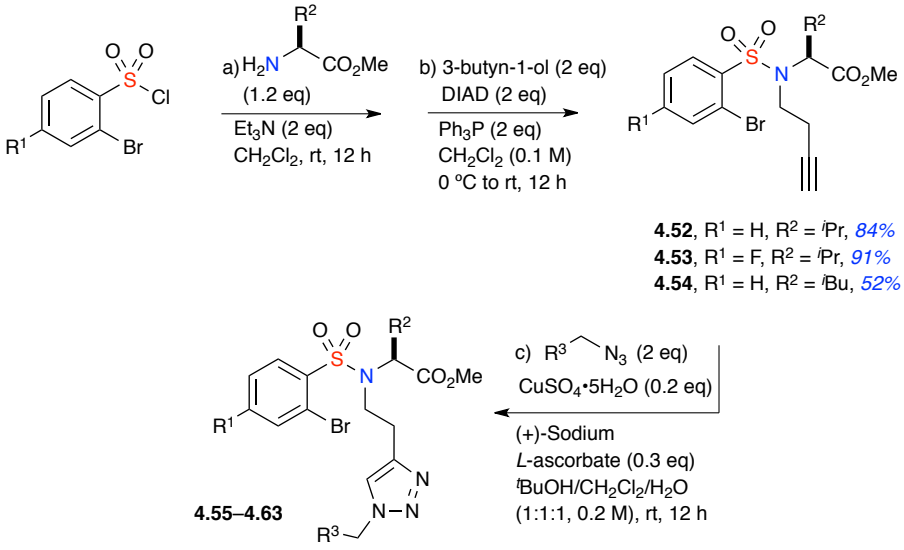
Entry	R^1	R^2	R^3	Product	Yield
1	H	^{i}Pr	Ph	**4.40**	67%
2	H	^{i}Pr	4-CH_3-Ph	**4.41**	54%
3	H	^{i}Pr	Cy	**4.42**	66%
4	H	^{i}Bu	Ph	**4.43**	60%
5	H	^{i}Bu	4-CH_3-Ph	**4.44**	33%
6	H	^{i}Bu	Cy	**4.45**	48%
7	F	^{i}Pr	Ph	**4.46**	34%
8	F	^{i}Pr	4-CH_3-Ph	**4.47**	31%
9	F	^{i}Pr	Cy	**4.48**	36%
10	F	^{i}Bu	Ph	**4.49**	25%
11	F	^{i}Bu	4-CH_3-Ph	**4.50**	86%
12	F	^{i}Bu	Cy	**4.51**	51%

4.2.3 Synthesis of 8-Membered Tricyclic, Biaryl Sultams Derived from Chiral, Non-racemic Amino Esters

With the previous results in hand, we extended the *C*-arylation reaction to access tricyclic, biaryl sultams of larger ring size. 3-Butyn-1-ol was used to introduce a distal homopropargyl group for ring extension. After sulfonylation with the respective *L*-amino methyl ester under standard conditions, the secondary

2-bromobenzenesulfonamide was subjected to Mitsunobu reaction conditions [3-butyn-1-ol, DIAD, Ph_3P, CH_2Cl_2, rt] to achieve homopropargyl benzenesulfonamides (**4.52**–**4.54**). Huisgen [3+2]-cycloaddition with three different

Table 4.3

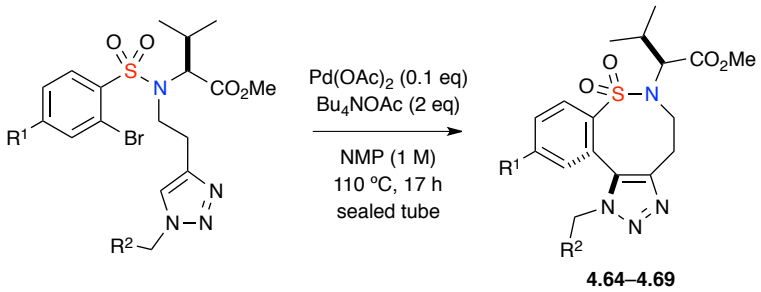


Entry	R^1	R^2	R^3	Product	Yield
1	H	^{i}Pr	Ph	**4.55**	78%
2	H	^{i}Pr	4-CH_3-Ph	**4.56**	82%
3	H	^{i}Pr	Cy	**4.57**	81%
4	H	^{i}Bu	Ph	**4.58**	98%
5	H	^{i}Bu	4-CH_3-Ph	**4.59**	98%
6	H	^{i}Bu	Cy	**4.60**	86%
7	F	^{i}Pr	Ph	**4.61**	99%
8	F	^{i}Pr	4-CH_3-Ph	**4.62**	88%
9	F	^{i}Pr	Cy	**4.63**	98%

azides provided corresponding 1,2,3-triazole-containing benzenesulfonamides **4.55**– **4.60** in good isolated yields (Entries 1–6, Table 4.3).

With the successful generation of scaffolds, the *C*-arylation reactions were carried out with **4.55**–**4.63** to produce 8-membered sultams in the presence of Pd-catalyst. The results for *C*-arylation of *L*-valine ($R^2 = {}^{i}Pr$) methyl ester analogues were summarized in Table 4.4. The 2-bromobenzenesulfonamides **4.55**–**4.57** and **4.61**–**4.63** were subjected to *C*-arylation reaction under standard reaction condition. 8-Membered tricyclic sultams **4.64**–**4.66** were produced in 54–67% isolated yields. The 4-fluoro substituted benzenesulfonamides **4.61**–**4.63** were also converted to 8-membered sultams in 31–36% isolated yields. The ^{1}H NMR spectra of these isolated products showed the mixture of two inseparable compounds with ~10:1 ratio.

Table 4.4

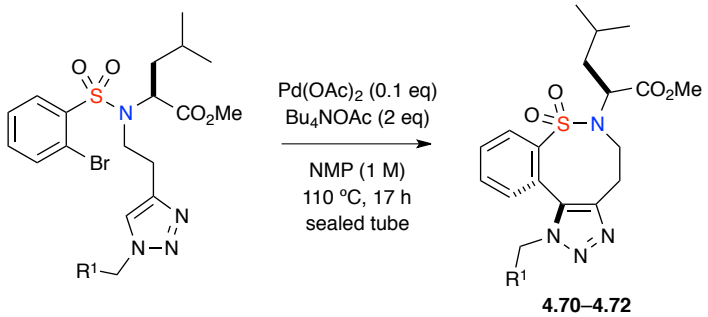


Entry	R^1	R^2	Product	Yield	Ratio[a] major:minor
1	H	Ph	**4.64**	67%	~10:1
2	H	4-CH_3-Ph	**4.65**	54%	~10:1
3	H	Cy	**4.66**	66%	~10:1
4	F	Ph	**4.67**	34%	~10:1
5	F	4-CH_3-Ph	**4.68**	31%	~10:1
6	F	Cy	**4.69**	36%	~10:1

[a] Ratio was determined from ^{1}H NMR spectra.

The *C*-arylation reactions to obtain 8-membered tricyclic, biaryl sultams derived from *L*-leucine methyl ester were next performed. Interestingly, all three reactions provided a 2:1 mixture of cyclized, inseparable products as evident by ^{1}H NMR (Table 4.5). The nature of this 2:1 mixture will be discussed at the end of this chapter.

Table 4.5



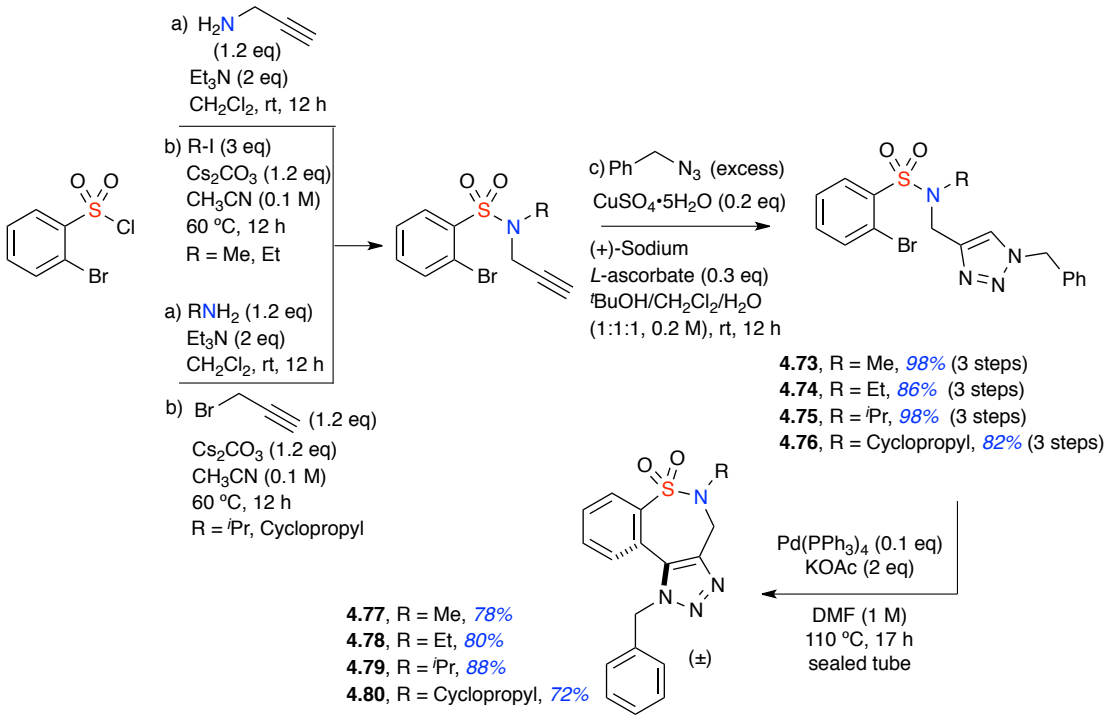
Entry	R^1	Product	Yield	Ratio[a] major:minor
1	Ph	**4.70**	60%	~2:1
2	4-CH_3-Ph	**4.71**	33%	~2:1
3	Cy	**4.72**	48%	~2:1

[a] Ratio was determined from ^{1}H NMR spectra.

4.2.4 Further Synthetic Applications of *C*-Arylation

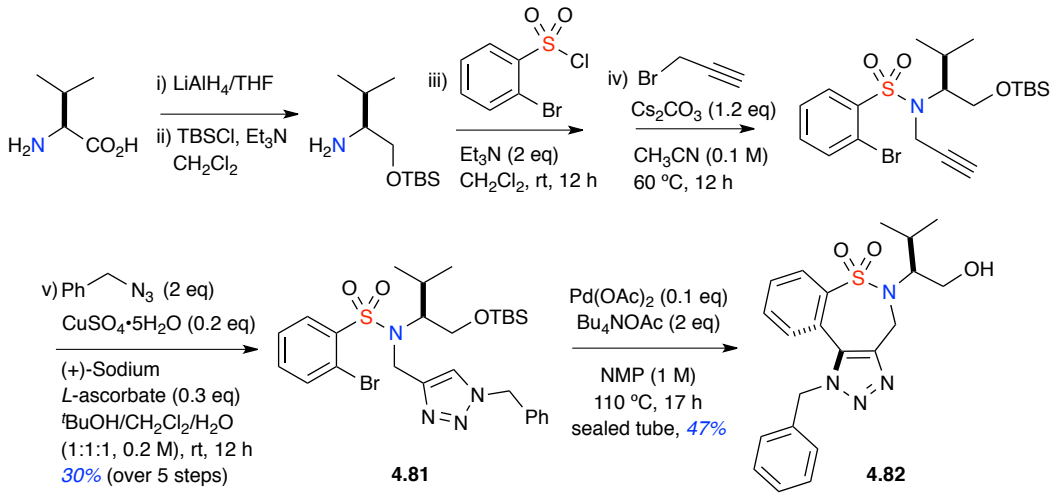
Based on previous results, several *N*-alkyl substituted 7-membered sultam compounds were also obtained from this *C*-arylation reaction process. The tertiary 2-bromobenzenesulfonamides **4.73**–**4.76** were prepared with methyl, ethyl, isopropyl and cyclopropyl groups in good isolated yields (82–98% over 3 steps). The triazole-containing, tertiary benzenesulfonamides were converted to the 7-membered tricyclic sultams **4.77**–**4.80,** in the presence of $Pd(PPh_3)_4$ catalyst, in 72–88% isolated yields (Scheme 4.5). Because Mitsunobu alkylation, as well as homopropargylation, did not proceed with secondary alkyl benzenesulfonamides, access to *N*-alkylated

8-membered sultams was not possible via this particular reaction sequence. The origins of these failed reactions are not clear at this time.



Scheme 4.5

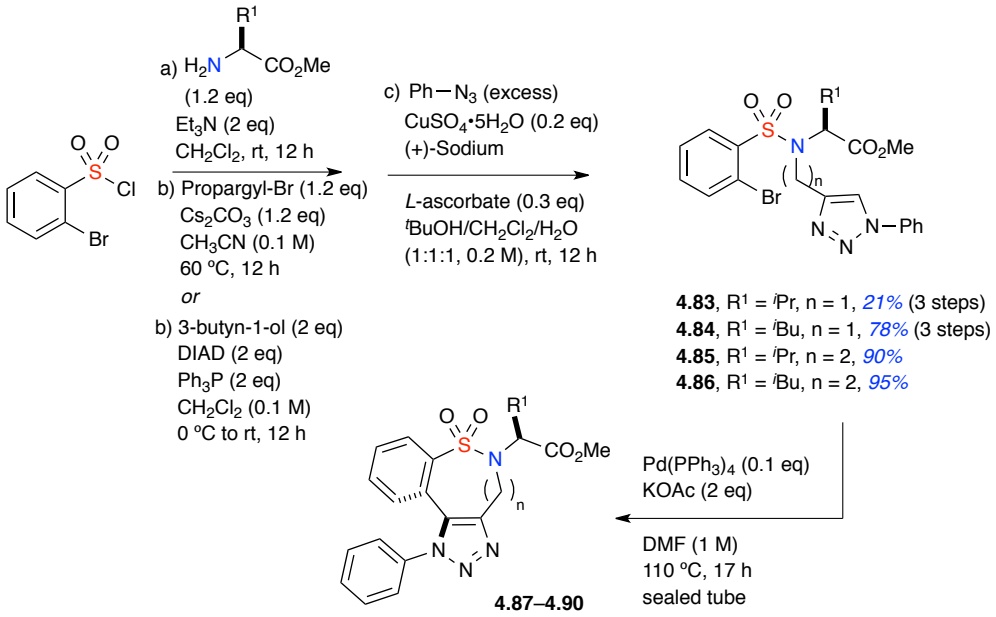
A 7-membered tricyclic sultam (**4.82**) derived from a chiral, non-racemic amino alcohol was also synthesized. TBS-protected *L*-valinol was synthesized from *L*-valine over 2 steps. TBS-protected 2-bromobenzenesulfonamide **4.81** was subjected to cyclization reaction in the presence of $Pd(OAc)_2$ to obtain the desired sultam **4.82** in 47% yield as a primary alcohol resulting from deprotection of TBS group during the reaction (Scheme 4.6).



Scheme 4.6

The 7- and 8-membered tricyclic sultams containing a phenyl-substituted triazole were also produced using this *C*-arylation pathway. The secondary 2-bromobenzenesulfonamides were prepared using the same reaction sequences from the previous reaction. The phenyl azide was prepared freshly starting from aniline in 3 steps.[19] Huisgen [3+2]-cycloaddition reactions were performed under standard reaction condition as mentioned earlier to provide the corresponding benzenesulfonamides **4.83**–**4.86** in 21–95% isolated yields, (Table 4.6).

Table 4.6



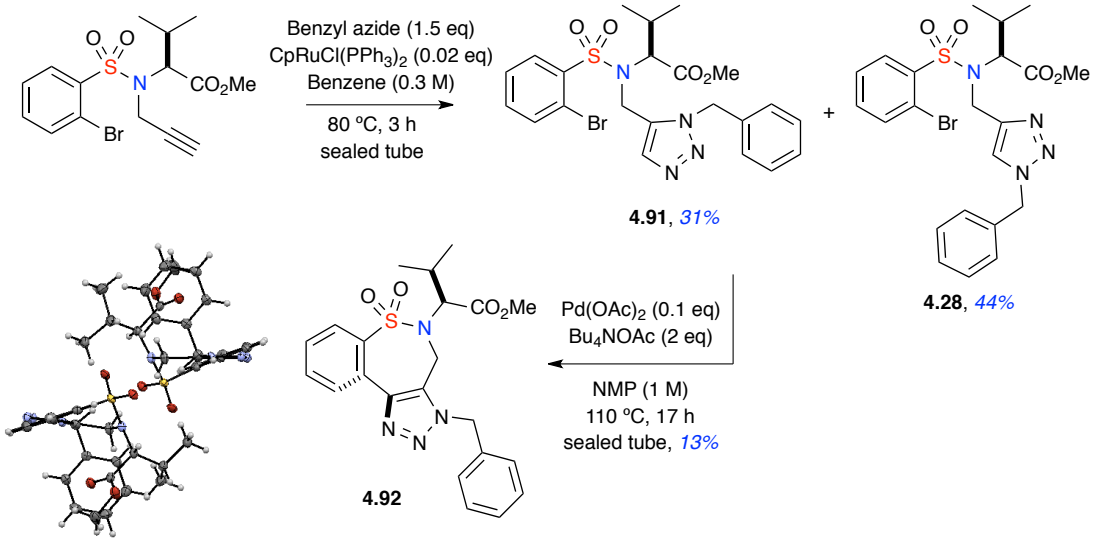
Entry	R^1	n	Product	Yield[a]
1	^{i}Pr	1	**4.87**	60%
2	^{i}Bu	1	**4.88**	46%
3	^{i}Pr	2	**4.89**	44% (~ 10:1)[b]
4	^{i}Bu	2	**4.90**	49% (~ 2:1)[b]

[a] based on recovered starting material; [b]Ratio (major:minor) was determined from ^{1}H NMR.

7-Membered tricyclic compounds **4.87** and **4.88** were obtained from Pd-catalyzed *C*-arylation in 60% and 46% yields based on recovered starting materials, respectively (Entries 1 and 2, Table 4.6). In contrast, cyclization reactions to 8-membered **4.89** and **4.90** gave a mixture of inseparable products in a similar ratio to that seen in the benzyl-substituted triazoles, *vide supra*. The ratio between major and minor products were around 10:1 ratio for *L*-valine methyl ester and around 2:1

ratio for *L*-leucine methyl ester, respectively, as observed by ^{1}H NMR. It is worth noting that the similarity in the ratio of products (10:1 and 2:1) in the benzyl- and phenyl-substituted triazoles was the same for **4.64** and **4.70**.

Study on the *C*-arylation of regioisomeric, 1,5-triazole benzenesulfonamide **4.91** was also performed. 1,5-Triazole benzenesulfonamide **4.91** was prepared in the presence of $CpRuCl(PPh)_3$ catalyst.[14b] The 1,5-triazole benzenesulfonamide **4.91** was obtained in 31% isolated yield as a minor product and the reaction still provided the 1,4-triazole benzenesulfonamide **4.28** as a major product (44% isolated yield). The 1,5-triazole benzenesulfonamide **4.91** was subjected to standard cyclization reaction generating the corresponding 7-membered tricyclic sultam **4.91** in 13% yield. We were able to obtain an X-ray structure of compound **4.92** (Scheme 4.7).



Scheme 4.7

4.2.5 X-ray and NMR Studies on Tricyclic, Biaryl Sultam Compounds

4.2.5.1 X-ray Structures

Among the series of tricyclic sultam compounds, several X-ray structures were obtained, with six of them presented in Figure 4.4. Several interesting structural characteristics were noted from these X-ray structures. Firstly, all six X-ray structures show the aforementioned axis of chirality between the benzene ring and the triazole ring in the solid phase. In addition, all amino ester-derived systems displayed "like" stereochemistry (S,S_a) between the external stereogenic center and biaryl axis

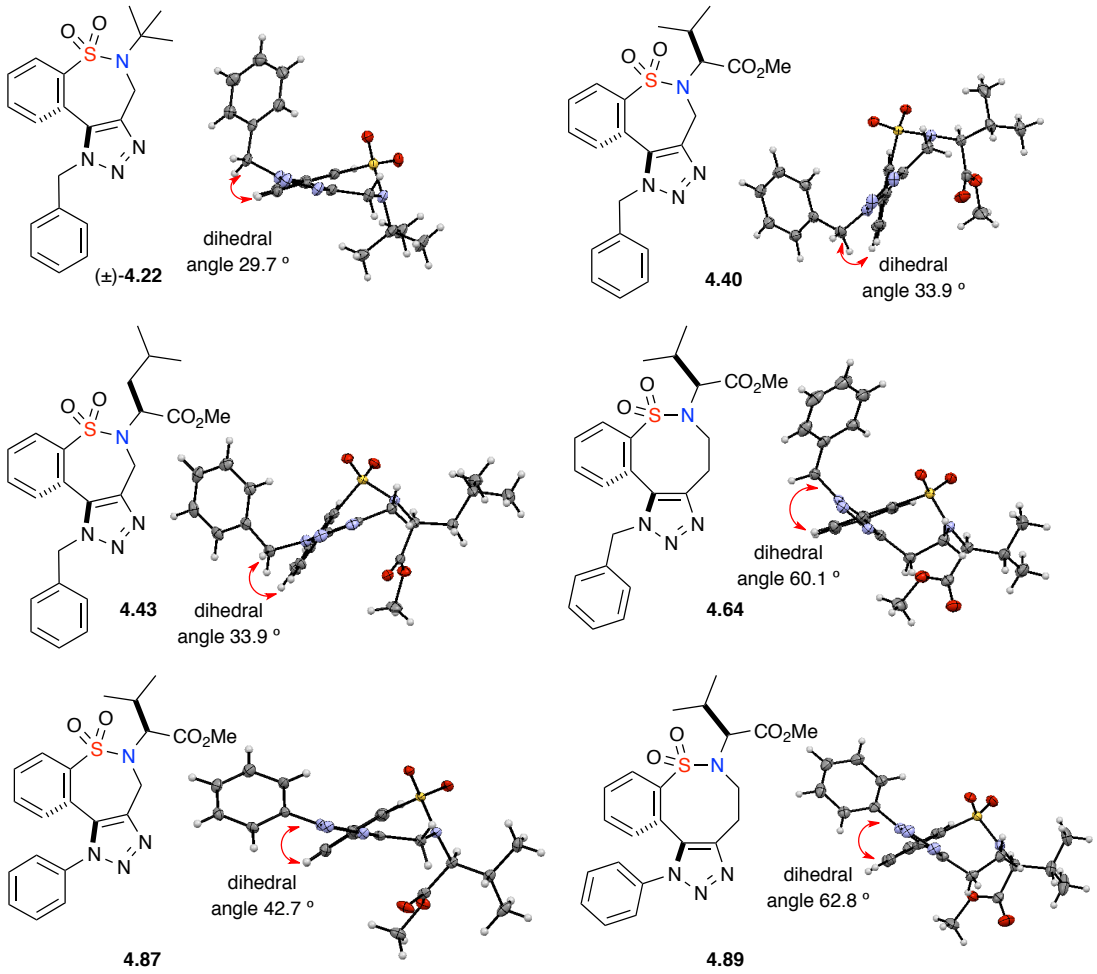


Figure 4.4

of chirality [and not "unlike" (S,R_a)]. Based on these structures, we also noticed the methyl group of the ester functionality (CO_2Me) was consistently positioned in a rotamer which placed it underneath the sultam benzene ring in all structures. This position is in agreement with anisotropic shielding by the phenyl group resulting in a notable upfield chemical shift of the methyl ester resonance (3.1–3.2 ppm) in its NMR spectrum, *vide infra*. Additionally, dihedral angles between two aryl rings are different depending on ring size as well as the triazole substituent. The dihedral angle of the 7-membered tricyclic sultam derived from *L*-leucine methyl ester was observed to be 34º. However, the dihedral angle for the 8-membered sultam **4.64** is approximately 60º. The dihedral angles for sultams with the phenyl group on the triazole (**4.87** and **4.89**) are bigger than the benzyl derivatives for both 7- and 8-membered sultams (Figure 4.4).

4.2.5.2 NMR Studies

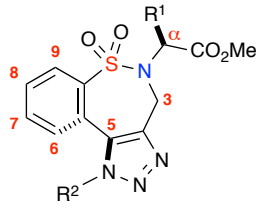
The chemical shifts of the methyl ester, the α-proton of the ester, and the two methyl groups within R^1 for the *L*-valine- and *L*-leucine-derived 7-membered sultams **4.40–4.45, 4.87** and **4.88** at room temperature are displayed in Table 4.7 (spectra are contained in the experimental section).

From this table, it can be seen that the average chemical shift of the α-proton of the ester is approximately 3.9 ppm and 4.5 ppm for the *L*-valine (R^1 = ^{i}Pr) and *L*-leucine (R^1 = ^{i}Bu) derivatives, respectively. Of notable importance, the chemical shift of the *L*-valine methyl esters (R^1 = ^{i}Pr) occurs at approximately 3.1 ppm, while

the corresponding *L*-leucine methyl esters ($R^1 = {}^{i}Bu$) occurs at approximately 3.3 ppm. These values are consistent with the aforementioned anisotropic shielding by the phenyl group, and when combined with the X-ray data, substantiates the existence of a preferred rotamer about the N–C bond in solution phase.

Detailed ^1H NMR studies at room temperature were next carried out on the 8-membered sultams **4.64** and **4.70** since the *C*-arylation reaction leading to both provided inseparable mixtures of products for *which no X-rays could be obtained* in the *L*-leucine-derived sultams (2:1 mixtures). We initially noticed a difference in the chemical shifts of the methyl ester resonance of the compound mixture for the *L*-valine- and *L*-leucine-derived sultams, **4.64** and **4.70**, respectively. The minor isomer occurs at 3.73 ppm in **4.64** and 3.76 ppm in **4.70**, while the major isomer displays upfield chemical shifts of 3.19 ppm and 3.25 ppm for **4.64** and **4.70**, respectively. For comparison purposes, detailed chemical shifts of particular protons from representative tricyclic, biaryl sultams can be found in the following Tables 4.7–4.9.

Table 4.7 *^{1}H NMR chemical shift data for the L-valine- (R^1 = ^{i}Pr) and L-leucine-derived (R^1 = ^{i}Bu), 7-membered sultams (single isomers, $CDCl_3$).*

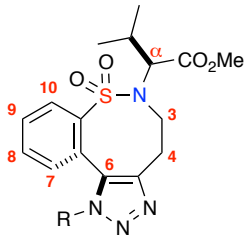


R^1	R^2	cmpd	*N*-C**H**$_2$ (ppm)	C3-C**H**$_2$ (ppm)	*α*-**H** (ppm)	$CO_2C\mathbf{H}_3$ (ppm)	2(C**H**$_3$) (ppm)	
^{i}Pr	Bn	**4.40**	5.82, 5.54	5.07, 5.02	3.92	3.10	1.05	0.91
^{i}Pr	4-Me-Bn	**4.41**	5.78, 5.48	5.06, 5.01	3.92	3.10	1.05	0.91
^{i}Pr	Cy-CH_2-	**4.42**	4.41, 4.29	5.02, 4.94	3.94	3.16	1.04	0.91
^{i}Pr	Ph	**4.87**	n/a	5.15, 5.10	3.93	3.11	1.08	0.92
^{i}Bu	Bn	**4.43**	5.82, 5.60	4.93, 4.83	4.57	3.32	0.95	0.93
^{i}Bu	4-Me-Bn	**4.44**	5.75, 5.53	4.91, 4.81	4.56	3.30	0.93	0.91
^{i}Bu	Cy-CH_2-	**4.45**	4.40, 4.32	4.84, 4.74	4.58	3.34	0.94	0.92
^{i}Bu	Ph	**4.88**	n/a	5.01, 4.94	4.55	3.32	0.94	0.93

The representative chemical shifts of the 8-membered, *L*-valine-derived sultams **4.64**–**4.66** and **4.89** (which were all ~10:1 mixtures) are also summarized in Table 4.8. From Table 4.8, we noticed the aforementioned, significant chemical shift differences of the methyl ester (Me resonance) between the major and minor isomers.

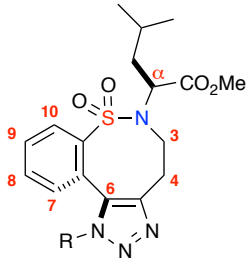
The chemical shifts of the methyl ester for each major isomer occur around ~3.2 ppm, while the minor isomers appear near ~3.7 ppm. This notable 0.5 ppm difference in methyl ester chemical shifts between major and minor isomers is augmented in an additional significant, but opposite, chemical shift trend for the two methyl groups in the alkyl side-chain (R^1 = ^{i}Pr) of **4.64**, whereby the major isomer occur further downfield (1.02/0.92 ppm) and the minor compound further upfield (0.85/0.41 ppm). These opposing trends continue for compounds **4.65**, **4.66** and **4.89** as well as for the 2:1 mixtures seen in all of the *L*-leucine-derived, 8-membered, tricyclic sultams (**4.70**–**4.72** and **4.90**) outlined in Table 4.9. Based on these chemical shift trends, we propose a major anisotropic shielding effect by the sultam benzene ring on both the methyl ester of the major isomer and the two diastereotopic methyl groups within each alkyl side chain of the minor isomer.

Table 4.8 *^1H NMR chemical shift data for the L-valine-derived, 8-membered sultams (major:minor = 10:1, $CDCl_3$).*



		α-H		$CO_2C\mathbf{H_3}$		2($C\mathbf{H_3}$)			
R	cmpd	major (ppm)	minor (ppm)	major (ppm)	minor (ppm)	major (ppm)		minor (ppm)	
Bn	**4.64**	4.00	4.07	3.19	3.73	1.02	0.92	0.85	0.41
4-Me-Bn	**4.65**	4.00	4.07	3.18	3.73	1.02	0.92	0.85	0.41
Cy-CH_2-	**4.66**	4.06	4.13	3.22	3.74	1.04	0.93	0.87	0.45
Ph	**4.89**	4.14	4.19	3.24	3.76	1.09	0.96	0.89	0.52

Table 4.9 *^{1}H NMR chemical shift data for the L-leucine-derived, 8-membered sultams (major:minor = 2:1, $CDCl_3$).*



		α-H		$CO_2C\mathbf{H_3}$		2($C\mathbf{H_3}$)			
R	cmpd	major (ppm)	minor (ppm)	major (ppm)	minor (ppm)	major (ppm)		minor (ppm)	
Bn	**4.70**	4.60	4.52	3.25	3.76	0.99	0.98	0.70	0.69
4-Me-Bn	**4.71**	4.60	4.53	3.24	3.76	0.99	0.98	0.71	0.69
Cy-CH_2-	**4.72**	4.66	4.58	3.28	3.76	1.01	0.99	0.73	0.72
Ph	**4.90**	4.72	4.65	3.29	3.80	1.03	1.01	0.75	0.74

The aforementioned opposing chemical trends in the major and minor isomers of the 2:1 inseparable mixtures, contained in Table 4.9, led us to perform a detailed 1D selective NOESY (Nuclear Overhauser Effect Spectroscopy) and ROESY (Rotating frame Overhauser Effect Spectroscopy) experiments on sultam **4.70** in order to uncover the identity of the major/minor isomers produced in the cyclization reactions leading to the *L*-leucine-derived, 8-membered sultams.

Given the molecular mass of these molecules, the NOESY and ROESY should be equivalent, though, in our hands, the signal-to-noise ratio is higher in the 1D selective ROESY spectra. The results of a series of 1D ROESY experiments

recorded with various mixing times (50-500 ms) and offset of the selective pulse are summarized in Figure 4.5. The arrow indicates a signal enhancement of the resonance at the *tip* of the arrow upon selective inversion of the resonance at the *end* of the arrow. As shown below, selective inversion of the aromatic proton at C7 results in enhancement of the methyl ester of the major product, the amino ester δ-proton residing in the alkyl side chain of the minor product, and the amino ester α-proton in both observed isomers. This result is consistent with the opposing anisotropic effects seen in the ^{1}H NMR trends outlined above, as well as the X-ray data highlighted in Figure 4.4. Taken collectively, these experimental findings identify the 2:1 mixture in the *L*-leucine-derived 8-membered sultam systems as a distribution of rotamers about the exocyclic N–Cα bond.

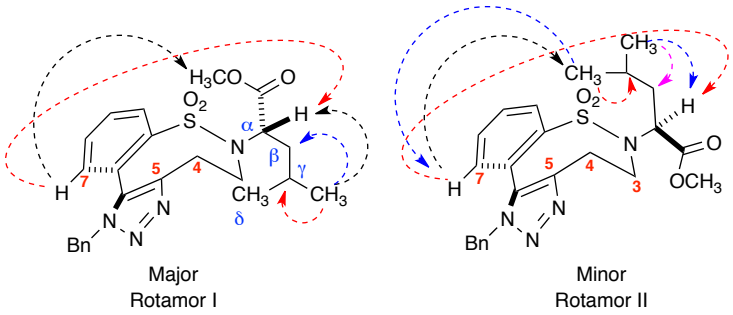


Figure 4.5 *ROESY results for sultam **4.70**.*

Though the X-ray structures show an axis of chirality between the benzene and triazole moieties of each sultam, data obtained from the previously described room temperature ^{1}H NMR studies were insufficient to confirm or deny the existence of a single atropdiastereomer or the rapid interconversion between two conformers of similar energy. Because room temperature ^{1}H NMR showed only one set of peaks for

both the *L*-valine-derived and *L*-leucine-derived 7-membered sultams, both extremes—high energy barrier or low energy barrier—could be operative. Thus, several temperature-variable NMR experiments, involving a variety of sultam substrates, were conducted to quantitate the energy barrier associated with this interconversion of atropdiastereomers.

The first assumption was that the energy barrier is very low and thus lowering the temperature will affect the rate of atropdiastereomer interconversion with a chance to observe resonance splitting corresponding to the "unlike" conformer (S,R_a). The first low temperature NMR study was carried out using *L*-valine-derived, 7-membered sultam **4.40** in acetone-d_6 as a NMR solvent and overlay spectrum showed in Figure 4.6.

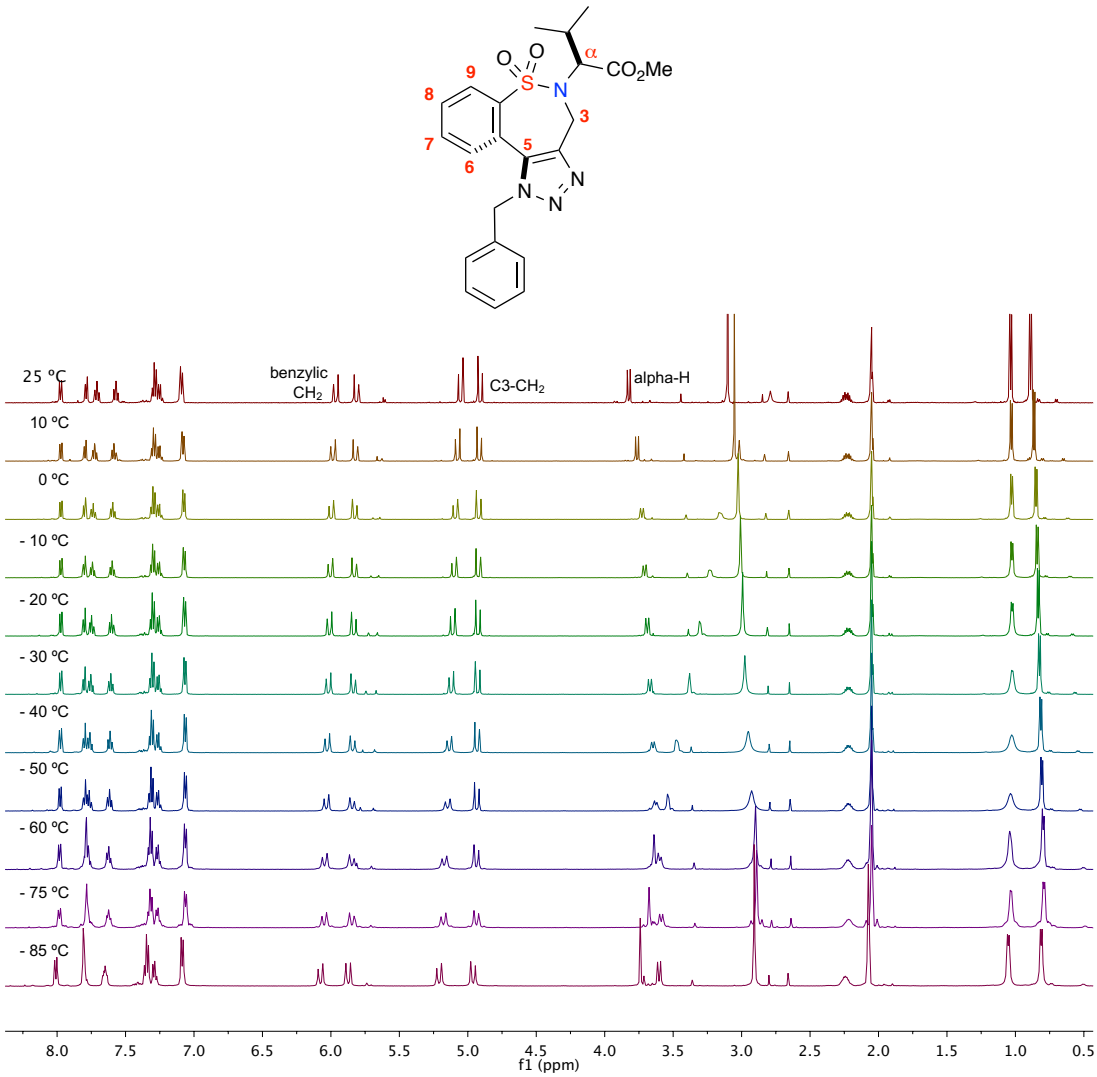
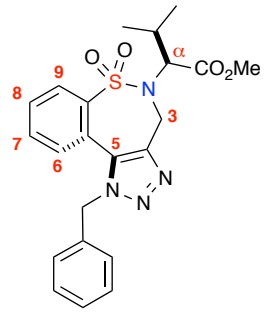


Figure 4.6 *Overlay from low temperature NMR study (**4.40**, Acetone-d_6).*

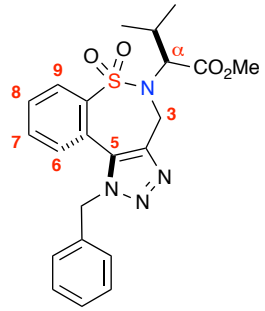
The representative chemical shifts from low temperature NMR studies are summarized in Tables 4.10A and 4.10B. As shown below, while temperatures were lowered to -85 ºC, no peak splitting or significant peak broadening was observed (except for the methyl at 1.1 ppm), leading us to proceed forth with high temperature experiments.

Table 4.10A *^{1}H NMR chemical shift data from low temperature NMR studies for the L-valine-derived, 7-membered sultam* ***4.40*** *(Acetone-d_6).*



	Benzylic CH_2 (ppm)		C3–CH_2 (ppm)		α-H (ppm)	CO_2CH_3 (ppm)	2(CH_3) (ppm)	
25 ºC	5.96	5.81	5.05	4.91	3.82	3.10	1.03	0.89
10 ºC	5.98	5.82	5.07	4.92	3.76	3.05	1.03	0.86
0 ºC	6.00	5.83	5.09	4.92	3.73	3.02	1.03	0.85
-10 ºC	6.00	5.83	5.10	4.92	3.71	3.01	1.03	0.84
-20 ºC	6.01	5.83	5.11	4.93	3.69	2.95	1.02	0.83
-30 ºC	6.02	5.84	5.12	4.93	3.66	2.98	1.02	0.82
-40 ºC	6.03	5.84	5.13	4.93	3.64	2.95	1.03	0.81
-50 ºC	6.03	5.84	5.15	4.93	3.64	2.93	1.04	0.81
-60 ºC	6.05	5.85	5.17	4.94	3.60	2.90	1.04	0.80
-75 ºC	6.05	5.84	5.18	4.94	3.59	2.89	1.04	0.78
-85 ºC	6.05	5.85	5.18	4.94	3.58	2.89	1.03	0.79

Table 4.10B *^{1}H NMR chemical shift data from low temperature NMR studies for the L-valine-derived, 7-membered sultam **4.40** (Acetone-d_6).*

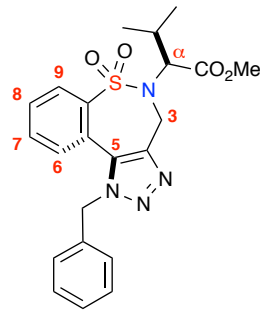


	C6–**H** (ppm)	C7–**H** (ppm)	C8–**H** (ppm)	C9–**H** (ppm)
25 ºC	7.97	7.57	7.71	7.79
10 ºC	7.97	7.58	7.72	7.79
0 ºC	7.97	7.60	7.74	7.80
-10 ºC	7.97	7.60	7.74	7.80
-20 ºC	7.97	7.60	7.75	7.80
-30 ºC	7.97	7.61	7.75	7.80
-40 ºC	7.97	7.61	7.76	7.80
-50 ºC	7.98	7.62	7.76	7.80
-60 ºC	7.98	7.62	7.76	7.79
-75 ºC	7.98	7.62	7.76	7.78
-85 ºC	7.99	7.63	7.78	7.79

Since no absolute conclusions could be drawn from the low temperature NMR studies discussed above, we moved onto the high temperature NMR studies with sultam **4.40**. In order to verify that thermodynamic equilibration had been fully achieved, the sample was heated for 24 hours at 210 ºC in benzene-d_6, cooled to room temperature and resubmitted to room temperature NMR evaluation which showed no

change in the spectrum indicating that thermodynamic equilibration had fully proceeded. In addition, detailed chemical shift trends for temperatures up to 125 ºC are highlighted in Tables 4.10A and 4.10B. From this experiment we noted peak shifting as a function of temperature. The difference of chemical shift for the methyl group is 0.23 ppm between room temperature and 125 ºC. In addition, the resonance of the α-proton shifted downfield at 125 ºC.

Table 4.11A *^{1}H NMR chemical shift data from high temperature NMR studies for the L-valine-derived, 7-membered sultam (**4.40**, DMSO-d_6).*

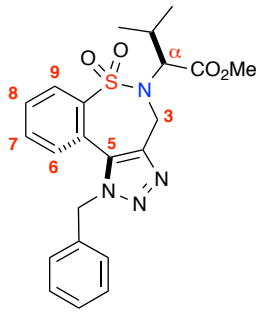


	Benzylic CH_2 (ppm)		C3–H_2 (ppm)		α-H (ppm)	CO_2CH_3 (ppm)	2(CH_3) (ppm)	
25 ºC	5.94	5.84	5.00	4.86	3.73	3.05	0.93	0.82
35 ºC	5.93	5.83	4.98	4.85	3.76	3.08	0.94	0.83
45 ºC	5.92	5.82	4.97	4.85	3.80	3.11	0.94	0.85
55 ºC	5.91	5.82	4.95	4.84	3.83	3.14	0.95	0.87
65 ºC	5.90	5.81	4.95	4.84	3.86	3.18	0.95	0.88
75 ºC	5.89	5.81	4.94	4.83	3.89	3.18	0.95	0.89

85 ºC	5.88	5.80	4.93	4.83	3.91	3.21	0.96	0.90
95 ºC	5.88	5.80	4.92	4.83	3.94	3.23	0.96	0.91
115 ºC	5.86	5.79	4.92	4.82	3.98	3.26	0.97	0.93
125 ºC	5.85	5.79	4.91	4.82	4.01	3.28	0.94	0.98

The distances between the AB quartet corresponding to each benzylic CH_2, as well as the C3-CH_2, also slightly decreased with increasing temperature (Table 4.11A) indicating no coalescence up to a temperature of 125 ºC. The chemical shifts for the four aromatic methine protons residing on C6–C9 are highlighted in Table 4.11B. As noted, only small variations of chemical shift were observed between rt and 125 ºC.

Table 4.11B *^1H NMR chemical shift data from high temperature NMR studies for the L-valine-derived, 7-membered sultam (**4.40**, DMSO-d_6).*



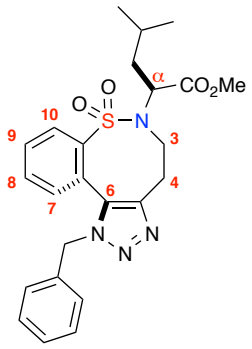
	C6–**H** (ppm)	C7–**H** (ppm)	C8–**H** (ppm)	C9–**H** (ppm)
25 ºC	7.90	7.56	7.71	7.85
35 ºC	7.90	7.56	7.71	7.84
45 ºC	7.91	7.56	7.70	7.83

55 ºC	7.91	7.56	7.70	7.82
65 ºC	7.92	7.56	7.70	7.81
75 ºC	7.92	7.56	7.69	7.80
85 ºC	7.93	7.56	7.69	7.80
95 ºC	7.93	7.55	7.69	7.79
115 ºC	7.94	7.55	7.68	7.78
125 ºC	7.94	7.55	7.68	7.77

Taken collectively, with the aforementioned low temperature studies, only minor variations of chemical shift were observed between temperatures ranging from -85 ºC to 125 ºC, and thus we postulate that the energy barrier of interconversion lies below 10 kcal/mol.[20]

With these studies in hand, we next performed high temperature NMR studies using the 2:1 mixture of rotamers in the 8-membered sultam **4.70**. Several ^{1}H NMR spectra were obtained between room temperature and 95 ºC (Table 4.12). While the diastereotopic benzylic CH_2 protons of the major compound coalesced at 65 ºC, no other coalescence was observed (Table 4.12).

Table 4.12 *^{1}H NMR chemical shift data from high temperature NMR studies for the L-leucine-derived, 8-membered sultam (**4.70**, DMSO-d_6).*



	Benzylic C**H**$_2$		α-**H**		CO_2C**H**$_3$		2(C**H**$_3$)	
	major (ppm)	minor (ppm)	major (ppm)	minor (ppm)	major (ppm)	minor (ppm)	major (ppm)	minor (ppm)
25 ºC	5.51, 5.46	5.75, 5.50	4.51	4.38	3.20	3.69	0.93	0.66, 0.63
45 ºC	5.51, 5.46	5.73, 5.50	4.52	4.39	3.21	3.69	0.94	0.67, 0.64
55 ºC	5.50, 5.46	5.72, 5.49	4.52	4.39	3.22	3.69	0.95	0.68, 0.65
65 ºC	5.47 (s)	5.70, 5.49	4.52	4.39	3.23	3.70	0.95	0.68, 0.66
75 ºC	5.47 (s)	5.69, 5.49	4.52	4.40	3.24	3.70	0.95	0.70, 0.67
85 ºC	5.47 (s)	5.68, 5.48	4.52	4.41	3.24	3.70	0.96	0.70, 0.68
95 ºC	5.47 (s)	5.67, 5.47	4.53	4.42	3.25	3.70	0.96	0.70

In order to ascertain the effect of steric bias in the external side chain on the interconversion barrier, we performed additional low temperature NMR studies with sultam **4.79** containing the *N*-isopropyl group. In theory, the achiral nature of the *N*-alkyl side chain renders any peak coalescence or splitting in this system to be a direct result of axial chirality interconversion and thus allow for quantitation of the

atropisomer interconversion barrier. Thus, several ^{1}H NMR spectra were obtained at various temperatures in acetone-d_6 as an NMR solvent. The overlay spectra is shown in Figure 4.7.

At 25 ºC, the spectra showed two singlets corresponding to the C3–CH_2 and benzylic CH_2 at 5.64 ppm and 4.80 ppm, respectively, while the isopropyl methyl resonance appeared as a doublet at 0.97 ppm. At -55ºC, all three peaks are broad singlets for each proton. At -75 ºC and -82 ºC, the benzylic CH_2 resonance divides into two broad singlets at 6.10 and 5.91 ppm, C3–CH_2 divides into two broad singlets at 5.00 and 4.80 ppm, and the isopropyl CH_3 also divides into two broad singlets at 1.23 and 0.51 ppm. Thus, at -82 ºC all signals are in slow-exchange on the NMR timescale. At low temperature, rotation about the N–Cα bond slows, causing the two methyl groups in the isopropyl side chain to have inequivalent chemical shifts, as only one methyl group is influenced by the aforementioned anisotropic shielding of the benzene ring which leads to an upfield chemical shift. Likewise, the benzylic CH_2 signal splits into two singlets as low temperature renders the methylene protons diastereotopic. These resonances divide into two separate broad singlets at low temperature because of a temperature-dependent decrease in the first order rate constants for inversion about the plane of symmetry for compound **4.79** (Figure 4.8).

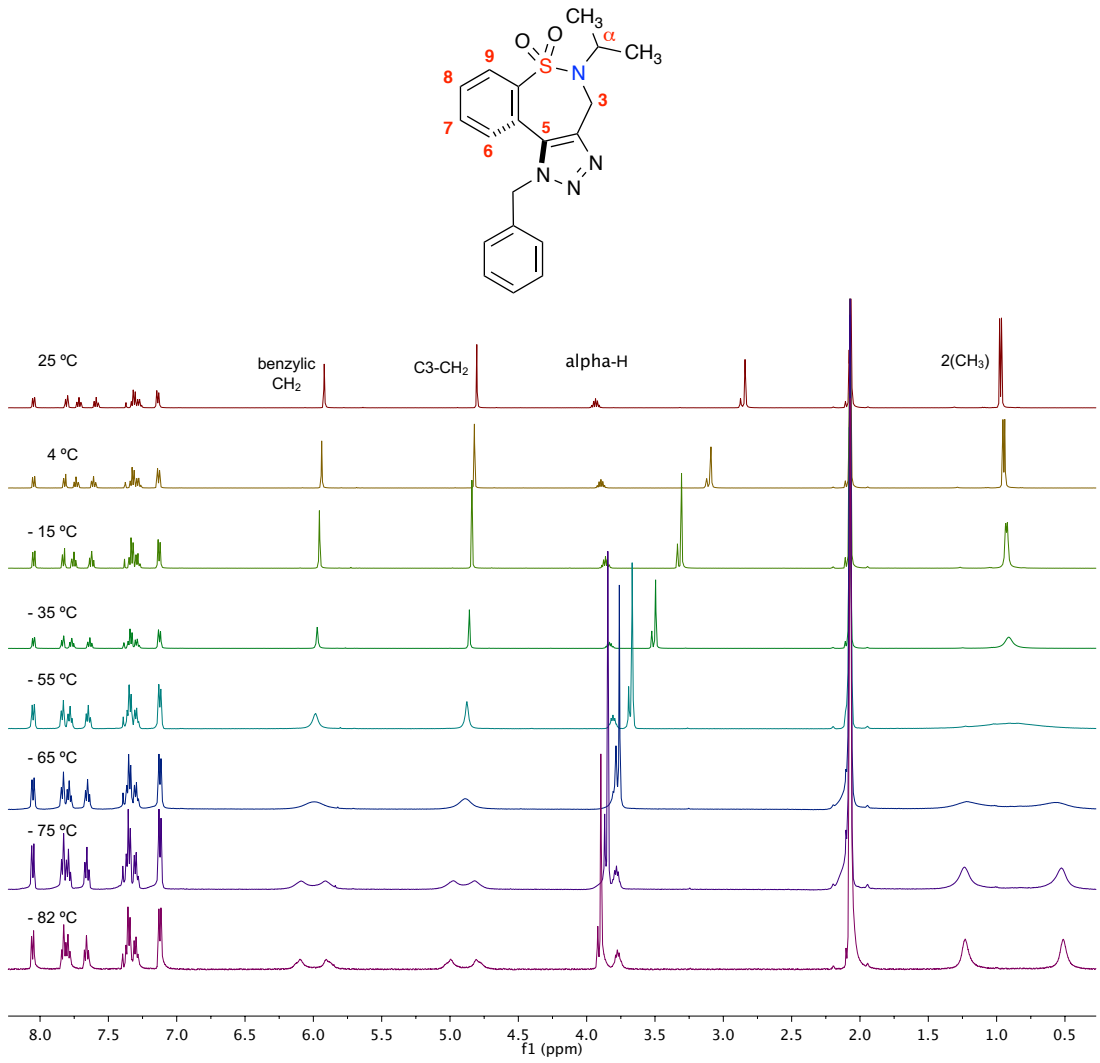


Figure 4.7 *Overlay from low temperature NMR study (**4.79**, Acetone-d_6).*

Moreover, as noted below, the rate constant and energy barrier could be calculated as outlined in Table 4.13. A value of ~ 10 kcal per mole in this isopropyl system is most likely similar to that in the valine-derived sultam **4.40** which substantiates the conclusion made earlier of a rapid equilibrating system under thermodynamic control.

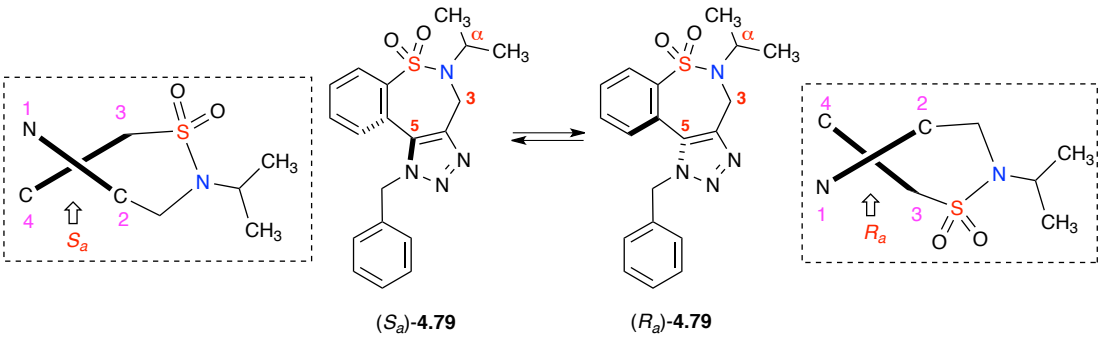


Figure 4.8

Table 4.13 *Rate constants and energy barriers.*

$$k = \frac{\pi\Delta\nu}{\sqrt{2}} \quad or \quad k = \frac{\pi}{\sqrt{2}}(\Delta\nu_{1/2} - \Delta\nu_{1/2}^{ref})$$

$$\Delta G = 2.303RT[10.32 + log\frac{T}{k}]$$

	2(CH_3)		C3-CH_2		*N*-CH_2	
	k	ΔG (kcal/mol)	*k*	ΔG (kcal/mol)	*k*	ΔG (kcal/mol)
-55 ºC	1410.47	9.48	199.86	10.32	333.18	10.10
-65 ºC	344.29	9.60	433.13	9.51	510.88	9.44
-75 ºC	755.22	8.82	144.39	9.47	166.59	9.41
-85 ºC	777.43	8.34	222.13	8.81	222.13	8.81

To test this hypothesis one more time, non-chiral tricyclic sultam **4.77** containing an *N*-methyl group was used for an additional low temperature NMR study, whereby diastereotopicity among the external side-chain is non-existent (Figure 4.9). We observed that it was not possible to reduce the temperature in the

NMR probe low enough to divide the C3-CH_2 or benzylic CH_2 singlets into two separate singlets. Thus, for this system, the rate constants for rotation about the triazole *N*-benzylic–C bond and the rate constants for atropisomer inversion are such that, even at -90 ºC, these signals are still in fast exchange on the NMR time scale. Nevertheless, both signals broaden significantly, indicating a trend towards the intermediate exchange regime. Efforts towards studying the conformational dynamics of the more sterically hindered, and symmetrical, *N*-^{t}Bu system, are in order and will be reported in due course.

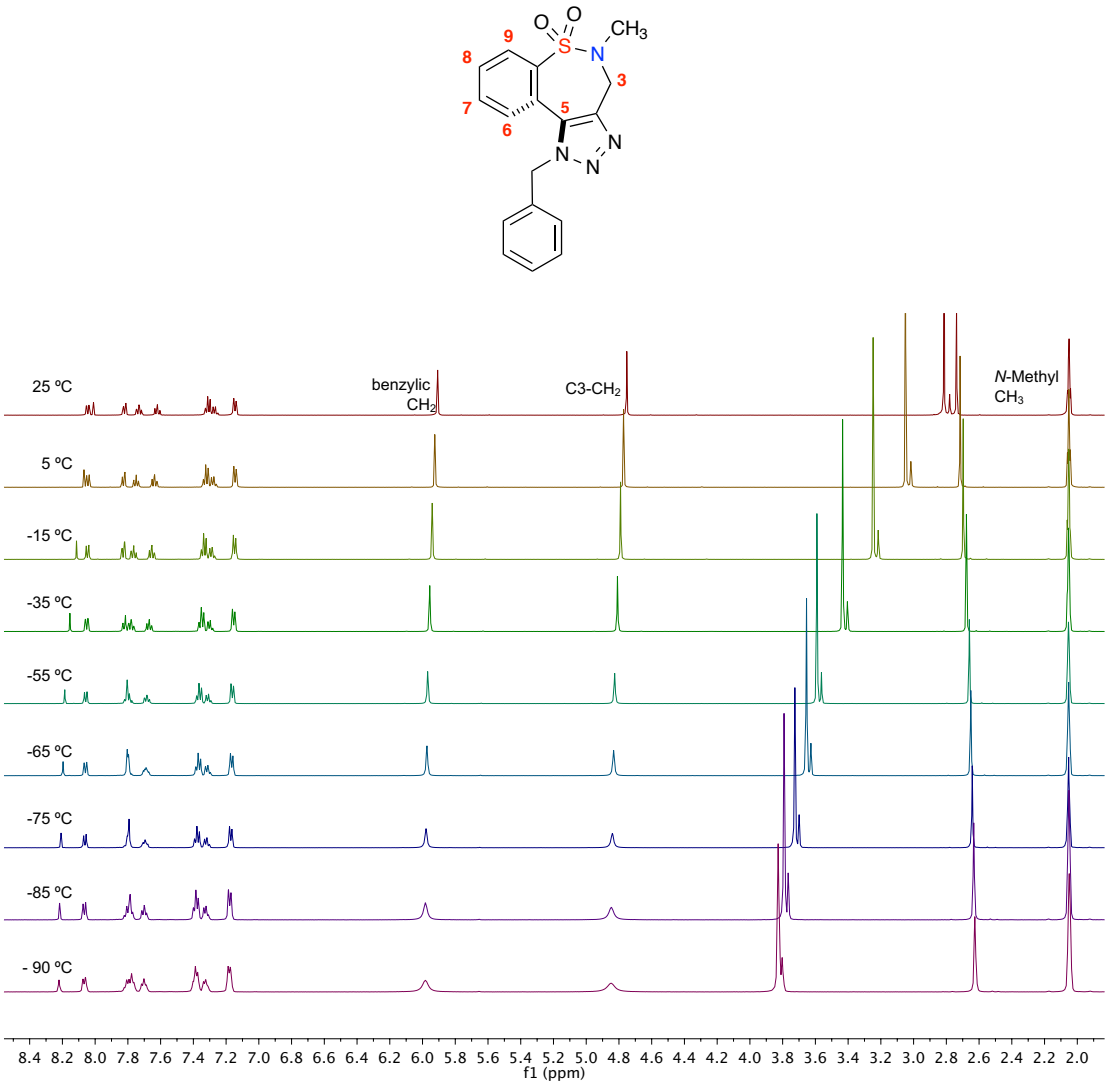


Figure 4.9 *Overlay from low temperature NMR study (**4.77**, Acetone-d_6).*

4.3 Conclusions

The synthesis of a collection of 7- and 8-membered tricyclic, biaryl sultams has been achieved using an intramolecular Pd-catalyzed *C*-arylation reaction of a triazole moiety. The cyclization reactions with alkyl-containing and chiral, non-

racemic amino ester-based tertiary sulfonamides furnished the corresponding 7-memberd tricyclic, biaryl sultams as a single conformer in a highly atropdiastereoselective thermodynamic equilibration process yielding a low energy conformer of "like" configuration (S,S_a). Furthermore, this Pd-catalyzed *C*-arylation reaction provided different conformational mixtures of 8-membered sultam products (10:1 and 2:1 for valine- and leucine-based systems, respectively).

In the course of X-ray crystallographic analysis, as well as detailed NMR studies, we uncovered a number of notable and interesting structural features of the 7-membered amino ester-derived sultams in both solid and solution phases that confirm a structure as a single conformer (>95:5) containing biaryl axial chirality of "like" configuration (S,S_a) with respect to the stereogenic center in the external side chain. Moreover, variable temperature NMR analysis has indicated that the axis of chirality at the biaryl bond has a relatively small interconversion barrier that allows for this rapid thermodynamic equilibration of the "like" and "unlike" atropdiastereomers. Detailed variable NMR analyses on a number of analogs, *vide infra*, point to rotamer dynamics (about the N–C bond in the external side chain) and ring size of the corresponding benzothiazepine (n = 1)/benzothiazocine (n = 2) 1,1-dioxides as governing factors in this notable thermodynamic equilibration of atropdiastereomers. Current efforts are focused on the computational calculation for the energy barrier between two atropdiastereomers interconversion, as well as the further development of an "atropdiastereoselective" *C*-arylation process. In addition, future studies will continue to probe the dynamic factors involved in the origins of

atropselectivity. Utilizing this methodology, we are also generating additional libraries of diverse tricyclic, biaryl sultams for high throughput screening of biological activity with our collaborators at the National Institutes of Health.

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Chapter 5

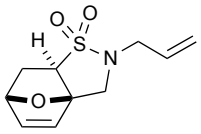
Experimental

5.1 General Experimental Methods

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannulas and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_3CN, CH_2Cl_2, THF and toluene were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 obtained from Sorbent Technologies (30930M-25, Silica Gel 60 Å, 40-63 μm). Metathesis catalysts were provided by Materia, Inc. and used without further purification. All protected glycidol compounds were provided from Daiso Co., Ltd., Fine Chemical Department. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively; or a Bruker Avance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

5.2 Experimental Data for Chapter 2

6*H*-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-allyl 1,1-dioxide [(±)-2.23]



Into a flame dried flask under argon was added furfurylamine (1.05 mL, 11.9 mmol), Et_3N (1.66 mL, 11.9 mmol), and dry CH_2Cl_2 (20 mL). After stirring at 0 ºC for 10 min, 2-chloroethanesulfonyl chloride (0.96 mL, 9.2 mmol) was added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was dissolved in dry CH_3CN (50 mL, 0.2 M) to which K_2CO_3 (3.9 g, 32.0 mmol) was added. After stirring for 5 mins, allyl bromide (2.8 mL, 32.0 mmol) was added and the reaction mixture was stirred at 60 ºC, until SM disappeared as monitored by TLC analysis. After such time, the crude reaction mixture was filtered through a pad of celite, concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to yield **2.23** (1.15 g, 5.0 mmol, 55%) as a white solid.

Mp 98 ºC;

FTIR (neat): 1442, 1301, 1068, 1137 cm^{-1};

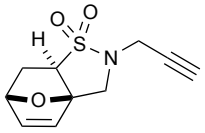
^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.53 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.37 (d, *J* = 5.7 Hz, 1H), 5.88 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.30 (ddq, *J* = 24.7, 10.1, 1.3 Hz, 2H), 5.23 (dd, *J* = 4.5, 1.7 Hz, 1H), 3.84 (d, *J* = 11.3 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.62 (d, *J* = 11.3 Hz, 1H), 3.18 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.61 – 2.55 (m, 1H), 1.81 (dd, *J* =

12.3, 7.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.5, 134.1, 132.4, 119.7, 90.5, 79.7, 60.5, 48.9, 47.6, 29.2;

HRMS calculated for $C_{10}H_{13}NO_3SNa$ $(M+Na)^+$ 250.0514, found 250.0518.

6*H*-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-propargyl, 1,1-dioxide [(±)-2.24]



Using the same procedure as that used to produce sultam **2.12**, *N*-(2-furanylmethyl)ethanesulfonamide (1.0 g, 5.28 mmol), propargyl bromide (2.8 ml, 32.0 mmol) yielded **2.13 (**68.9 mg, 3.0 mmol, 58%) as a white solid.

Mp 150 ºC;

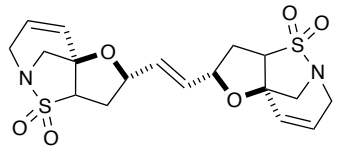
FTIR (neat): 3226, 1304, 1282, 1140 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.55 (dd, *J* = 1.7, 5.7 Hz, 1H), 6.42 (d, *J* = 5.7 Hz, 1H), 5.26 (dd, *J* = 4.5, 1.6 Hz, 1H), 4.10 – 4.02 (m, 2H), 3.93 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 3.18 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.37 (t, *J* = 2.5 Hz, 1H), 1.81 (dd, *J* = 12.4, 7.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.5, 134.1, 90.7, 79.8, 76.8, 74.1, 60.5, 48.8, 34.7, 29.1;

HRMS calculated for $C_{10}H_{11}NO_3SNa$ $(M+Na)^+$ 248.0357, found 248.0347.

(5a*R*,5a'*R*)-7,7'-((*E*)-Ethene-1,2-diyl)bis(3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide) [(±)-2.25]



To a flame dried flask was added dry CH_2Cl_2 (95 mL, 0.005 M), which was degassed for 30 min with argon. After such time, sultam **2.23** (0.1 g, 0.44 mmol) and cat-**B** (0.04 g, 0.044 mmol) were added and the reaction mixture was refluxed at 45 ºC for 3 h. The crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide **2.25** (15.7 mg, 0.36 mmol, 84% yield) as a white solid.

Mp 227 ºC;

FTIR (neat): 1336, 1164, 1112 cm^{-1};

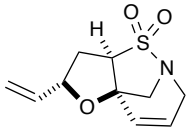
^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.28 (ddd, J = 10.1, 5.1, 2.1 Hz, 1H), 5.76 (ddd, J = 6.7, 3.4, 1.7 Hz, 1H), 5.55 (dt, J = 10.1, 2.5 Hz, 1H), 4.84 (d, J = 6.0 Hz, 1H), 4.19 (dt, J = 19.5, 2.5 Hz, 1H), 3.79 (dt, J = 19.6, 2.2 Hz, 1H), 3.71 (dd, J = 11.0, 5.7 Hz, 1H), 3.59 (dd, J = 12.2, 1.9 Hz, 1H), 3.24 (dd, J = 12.2, 1.8 Hz, 1H), 2.71 (dddd, J = 14.0, 8.1, 5.8, 2.1 Hz, 1H), 2.14 – 2.06 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.2, 134.2, 131.2, 130.9, 124.1, 124.1, 87.6, 80.9, 80.7, 71.0, 71.0, 51.9, 50.9, 34.1, 34.1;

HRMS calculated for $C_{18}H_{22}N_2O_6S_2Na$ $(M+Na)^+$ 449.0817, found 449.0816.

General Procedure A for ROM-RCM-CM Cascade: To a flame dried flask was added dry CH_2Cl_2 (0.005 M), which was degassed for 30 min with argon. To this was added, sultam (1 eq.), cat-**B** (10 mol%) and CM partner (10 eq.). The reaction mixture was refluxed at 45 ºC for 3 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane: EtOAc) to afford the desired compound.

(5a*R*,8a*R*)-7-Vinyl-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.26]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) was added to ethylene degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.26** (50 mg, 0.22 mmol, 74%) as a yellow solid.

Mp 91 ºC;

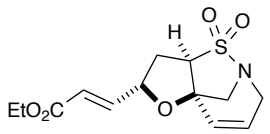
FTIR (neat): 2925, 1350, 1338, 1166 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.28 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.80 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.57 – 5.48 (m, 1H), 5.33 – 5.25 (m, 1H), 5.19 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.82 (dd, *J* = 14.6, 6.9 Hz, 1H), 4.18 (dt, *J* = 19.5, 2.4 Hz, 1H), 3.76 (dt, *J* = 19.5, 2.2 Hz, 1H), 3.70 (ddd, *J* = 10.9, 6.0, 1.9 Hz, 1H), 3.59 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.23 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.68 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 2.09 (ddd, *J* = 14.1, 10.9, 7.1 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.6, 133.5, 123.0, 116.4, 86.6, 81.4, 70.2, 51.1, 50.0, 33.0;

HRMS calculated for $C_{10}H_{13}NO_3SNa$ $(M+Na)^+$ 250.0514; found 250.0507.

(*E*)-Ethyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.27]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and ethyl acrylate (3.2 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.27** (58 mg, 0.19 mmol, 65%) as a pale yellow solid.

Mp 232 ºC;

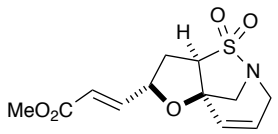
FTIR (neat): 1716, 1350, 1269, 1167 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.85 (dd, *J* = 15.6, 5.0 Hz, 1H), 6.30 (d, *J* = 10.1 Hz, 1H), 6.04 (d, *J* = 15.6 Hz, 1H), 5.57 (d, *J* = 10.1 Hz, 1H), 5.02 (dd, *J* = 13.4, 6.7 Hz, 1H), 4.24 – 4.16 (m, 3H), 3.82 – 3.75 (m, 1H), 3.75 – 3.69 (m, 1H), 3.62 – 3.56 (m, 1H), 3.30 – 3.25 (m, 1H), 2.83 – 2.74 (m, 1H), 2.21 – 2.12 (m, 1H), 1.32 – 1.27 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.9, 144.7, 134.0, 124.2, 121.7, 88.0, 80.0, 70.5, 60.8, 52.1, 51.0, 33.5, 14.2;

HRMS calculated for $C_{13}H_{17}NO_5SNa$ $(M+Na)^+$ 322.0725, found 322.0698.

(*E*)-Methyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.28]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and methyl acrylate (2.7 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.28** (48 mg, 0.16 mmol, 56%) as a pale yellow solid.

Mp 144 ºC;

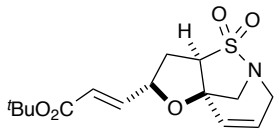
FTIR (neat): 1722, 1350, 1340, 1167 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.86 (d, *J* = 13.8 Hz, 1H), 6.30 (d, *J* = 8.0 Hz, 1H), 6.05 (d, *J* = 15.3 Hz, 1H), 5.56 (d, *J* = 7.9 Hz, 1H), 5.02 (s, 1H), 4.19 (d, *J* = 19.2 Hz, 1H), 3.85 – 3.53 (m, 6H), 3.28 (d, *J* = 11.6 Hz, 1H), 2.78 (s, 1H), 2.16 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.3, 145.0, 133.9, 124.2, 121.2, 88.0, 80.0, 70.5, 52.1, 51.9, 50.9, 33.5;

HRMS calculated for $C_{12}H_{15}NO_5SNa$ $(M+Na)^+$ 308.0569; found 308.0562.

(*E*)-*tert*-Butyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.29]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and *t*-butyl acrylate (4.3 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.29** (76 mg, 0.23 mmol, 78%) as a yellow oil.

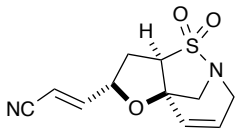
FTIR (neat): 2978, 1711, 1352, 1314, 1165 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.77 (dd, J = 15.6, 5.0 Hz, 1H), 6.34 (d, J = 10.2 Hz, 1H), 5.99 (d, J = 15.6 Hz, 1H), 5.59 (d, J = 10.3 Hz, 1H), 5.03 (s, 1H), 4.23 (d, J = 19.6 Hz, 1H), 3.87 – 3.71 (m, 2H), 3.62 (d, J = 12.5 Hz, 1H), 3.30 (d, J = 12.2 Hz, 1H), 2.80 (s, 1H), 2.19 (ddd, J = 14.0, 10.8, 6.6 Hz, 1H), 1.51 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.1, 143.4, 134.1, 124.2, 123.6, 88.0, 81.0, 80.1, 76.8, 70.6, 52.1, 50.9, 33.5, 31.0, 28.1;

HRMS calculated for $C_{15}H_{21}NO_5SNa$ $(M+Na)^+$ 350.1038, found 350.1030.

(*E*)-3-((5a*R*,8a*R*)-1,1-Dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylonitrile [(±)-2.30]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and acrylonitrile (1.9 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.30** (50 mg, 0.20 mmol, 67%) as a white solid.

Mp 170 ºC;

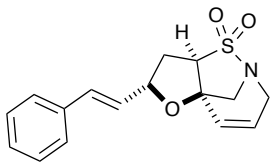
FTIR (neat): 1338, 1164, 1114 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.67 (dd, *J* = 16.2, 4.3 Hz, 1H), 6.28 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.67 (dd, *J* = 16.2, 1.9 Hz, 1H), 5.60 (dt, *J* = 10.1, 2.5 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.21 (dt, *J* = 19.6, 2.5 Hz, 1H), 3.80 (dt, *J* = 19.6, 2.2 Hz, 1H), 3.72 (ddd, *J* = 10.8, 6.4, 1.9 Hz, 1H), 3.58 (dd, *J* = 12.3, 2.0 Hz, 1H), 3.29 (dd, *J* = 12.3, 2.0 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.16 (ddd, *J* = 14.1, 10.9, 6.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.9, 132.3, 123.5, 115.4, 99.4, 87.1, 78.4, 69.1, 50.9, 49.9, 32.2;

HRMS calculated for $C_{11}H_{12}N_2O_3SNa$ $(M+Na)^+$ 275.0466, found 275.0468.

(5a*R*,8a*R*)-7-((*E*)-Styryl)-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.31]



According to general procedure **A**, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and styrene (3.4 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.31** (73 mg, 0.24 mmol, 81%) as a brown liquid.

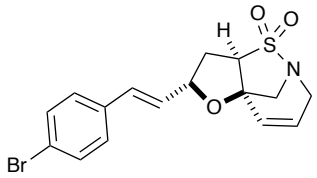
FTIR (neat): 1348, 1338, 1164, 1132, 968, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 (dd, *J* = 5.0, 3.4 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.28 (dt, *J* = 4.7, 1.9 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.34 (dq, *J* = 10.1, 2.1 Hz, 1H), 6.15 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.56 (dt, *J* = 10.1, 2.5 Hz, 1H), 5.01 (q, *J* = 7.2 Hz, 1H), 4.22 (dt, *J* = 19.5, 2.5 Hz, 1H), 3.84 – 3.74 (m, 2H), 3.66 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.28 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.78 (ddd, *J* = 13.9, 8.0, 5.7 Hz, 1H), 2.21 (ddd, *J* = 14.2, 11.1, 7.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.9, 134.4, 132.8, 128.9, 128.3, 127.3, 126.7, 124.0, 87.5, 82.2, 71.3, 51.9, 51.0, 34.4;

HRMS calculated for $C_{16}H_{17}NO_3SNa$ $(M+Na)^+$ 326.0827, found 326.0795.

(5a*R*,8a*R*)-7-((*E*)-4-Bromostyryl)-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.32]



According to general procedure, **2.23** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and 4-bromostyrene (3.9 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.32** (87 mg, 0.23 mmol, 80%) as a white solid.

Mp 140 ºC;

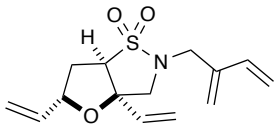
FTIR (neat): 1487, 1350, 1338, 1164, 744 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 – 7.43 (m, 2H), 7.25 (dt, *J* = 9.0, 2.2 Hz, 2H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.33 (dq, *J* = 10.1, 2.1 Hz, 1H), 6.14 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.57 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.99 (q, *J* = 7.1 Hz, 1H), 4.22 (dt, *J* = 19.5, 2.5 Hz, 1H), 3.84 – 3.73 (m, 2H), 3.65 (dd, *J* =12.2, 2.0 Hz, 1H), 3.28 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.77 (ddd, *J* = 13.9, 8.0, 5.7 Hz, 1H), 2.19 (ddd, *J* = 14.2, 11.1, 7.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.8, 134.3, 131.8, 131.5, 128.2, 128.1, 124.1, 122.1, 87.6, 81.9, 71.2, 51.9, 51.0, 34.3;

HRMS calculated for $C_{16}H_{16}BrNO_3SNa$ $(M+Na)^+$ 403.9932; found 403.9619.

(3a*R*,6a*R*)-2-(2-Methylenebut-3-en-1-yl)-3a,5-divinylhexahydrofuro[2,3-*d*]isothiazole 1,1-dioxide [(±)-2.34]



According to general procedure **A**, **2.24** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.34** (63 mg, 0.23 mmol, 75%) as a brown liquid.

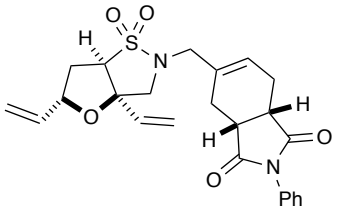
FTIR (neat): 2927, 1597, 1311, 1150, 931 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.36 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.99 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.57 – 5.44 (m, 2H), 5.33 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.28 – 5.16 (m, 5H), 4.71 – 4.65 (m, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.53 (d, *J* = 8.6 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.28 (d, *J* = 10.9 Hz, 1H), 3.10 (d, *J* = 10.9 Hz, 1H), 2.70 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.00 (ddd, *J* = 13.7, 10.8, 8.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.4, 137.3, 136.2, 136.0, 119.9, 118.1, 116.4, 115.7, 85.7, 81.8, 66.6, 56.7, 44.7, 35.1;

HRMS calculated for $C_{14}H_{19}NO_3SNa$ $(M+Na)^+$ 304.0983, found 304.0947.

(3a*R*,7a*S*)-5-(((3a*R*,6a*R*)-1,1-Dioxido-3a,5-divinyltetrahydrofuro[2,3-*d*]isothiazol-2(5*H*)-yl)methyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [(±)-2.35]



To a flame dried flask containing dry toluene (0.5 mL) was added diene **2.34** (30 mg, 0.1 mmol) and *N*-phenylmaleimide (0.23 g, 0.13 mmol). The reaction was heated at 85 ºC for 24 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (3:2 hexane:EtOAc) to yield **2.35** (38 mg, 8.3×10^{-5} mol, 83%) as a yellow oil.

FTIR (neat): 1709, 1498, 1383, 1309, 1147 cm^{-1};

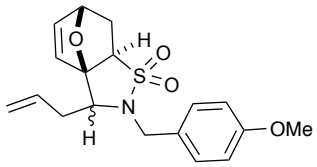
^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.43 (dd, *J* = 16.5, 8.0 Hz, 2H), 7.36 (dd, *J* = 15.2, 7.5 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 5.94 (td, *J* = 16.7, 10.8 Hz, 2H), 5.80 (dddd, *J* = 17.0, 13.4, 10.4, 6.8 Hz, 1H), 5.56 – 5.47 (m, 1H), 5.37 (dd, *J* = 22.0, 17.2 Hz, 1H), 5.28 – 5.13 (m, 2H), 4.79 – 4.71 (m, 1H), 3.81 (d, *J* = 14.1 Hz, 1H), 3.52 (d, *J* = 8.0 Hz, 1H), 3.42 – 3.22 (m, 3H), 3.16 (dd, *J* = 10.8, 5.5, Hz, 1H), 3.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.76 – 2.64 (m, 3H), 2.47 – 2.32 (m, 2H), 2.00 (ddd, *J* = 17.0, 14.1, 7.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 178.8, 178.7, 178.4 (2), 137.3, 137.2, 136.3, 136.2, 134.4, 134.0, 131.9 (2), 129.1, 129.0, 128.6, 128.5, 126.4 (2), 125.7, 125.6, 118.2, 117.8, 116.6, 116.5, 86.0, 85.7, 82.2, 81.7, 66.7 (2), 57.9, 57.0, 49.5, 49.2,

39.4, 39.0, 38.9 (2), 34.9, 34.8, 25.6 (2), 24.3, 24.1;

HRMS calculated for $C_{24}H_{26}N_2O_5SNa$ $(M+Na)^+$ 477.1460, found 477.1436.

(3a*R*,6*S*,7a*R*)-3-Allyl-2-(4-methoxybenzyl)-3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole 1,1-dioxide [(±)-2.37]



To a flame dried flask under argon was added furfural (1.72 mL, 20.8 mmol), 4-methoxybenzylamine (2.7 mL, 20.8 mmol), $MgSO_4$ (3.0 g) and dry CH_2Cl_2 (20 mL). After stirring at rt for 6 h, the crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was dissolved in THF (20 mL) to which was added allyl magnesium bromide (5.57 mL, 11.15 mmol). The reaction mixture was stirred for 5 h. after which time NH_4Cl (sat. aq., 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic layer was dried ($MgSO_4$). The crude reaction mixture **2.36** (1.2 g) was solvated in dry toluene (5 mL) and heated at reflux for 12 h. After such time the crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide the desired compound **2.37** (95%) as a yellow liquid.

FTIR (neat): 1612, 1514, 1301, 1247, 1137 cm^{-1};

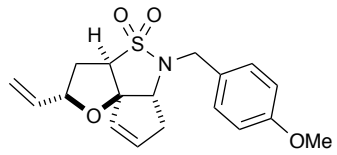
[Mixture of Diastereoisomers (1:1)] ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.95 – 6.81 (m, 4H), 6.52 (dd, J = 5.8, 1.7 Hz 1H), 6.47 – 6.38 (m, 3H), 6.18 (d, J = 5.7 Hz, 1H), 5.93 – 5.78 (m, 1H), 5.74 – 5.58 (m, 1H), 5.28 (dd, J = 4.5, 1.5 Hz 1H), 5.22 – 5.14 (m, 2H), 5.09 – 4.97 (m, 2H), 4.51 (d, J = 15.7 Hz, 1H), 4.41 (d, J = 15.3 Hz, 1H), 4.28 (dd, J = 15.5, 8.7 Hz 2H), 3.81

(dd, J = 8.9, 5.6 Hz, 6H), 3.72 (t, J = 5.3 Hz, 1H), 3.24 (dd, J = 7.9, 3.2 Hz, 1H), 3.13 (dd, J = 7.8, 3.3 Hz, 1H), 2.74 – 2.59 (m, 1H), 2.56 – 2.48 (m, 1H), 2.45 (t, J = 7.2 Hz, 1H), 1.80 (td, J = 12.4, 7.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.3, 159.2, 139.7, 137.9, 135.3, 132.9, 132.6, 132.1, 130.0, 129.9, 127.6, 127.3, 119.4, 118.9, 114.1, 114.1, 94.5, 92.2, 79.4, 78.8, 60.4, 59.7, 58.6, 58.4, 55.3, 55.3, 46.6, 46.0, 34.6, 33.8, 30.1, 29.5;

HRMS calculated for $C_{18}H_{21}NO_4SNa$ $(M+Na)^+$ 370.1089, found 370.1075.

(2*S*,3a*R*,5a*R*,8a*R*)-5-(4-Methoxybenzyl)-2-vinyl-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazole 4,4-dioxide [(±)-2.38]



According to general procedure **A**, **2.37** (0.06 g, 0.17 mmol), cat-**B** (0.015 g, 0.017 mmol) in ethylene degassed CH_2Cl_2 (35 mL). The crude reaction was purified by flash chromatography (2:1 hexane:EtOAc) to provide **2.38** (32 mg, 54%) and **2.39** (10 mg, 16%).

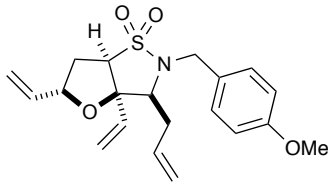
FTIR (neat): 1612, 1514, 1305, 1249, 1149 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.22 (m, 2H), 7.11 – 6.74 (m, 2H), 6.10 – 5.87 (m, 1H), 5.80 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1H), 5.72 (dt, *J* = 5.7, 2.2 Hz, 1H), 5.30 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.52 – 4.38 (m, 2H), 4.05 (d, *J* = 14.4 Hz, 1H), 3.82 (d, *J* = 5.2 Hz, 3H), 3.64 – 3.54 (m, 2H), 2.75 (ddd, *J* = 13.8, 5.5, 2.0 Hz, 1H), 2.64 – 2.43 (m, 2H), 2.12 (dt, *J* = 13.8, 9.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.5, 135.9, 135.1, 130.4, 130.2, 126.8, 118.0, 114.1, 97.3, 80.1, 64.6, 63.8, 55.3, 45.4, 35.5, 35.2;

HRMS calculated for $C_{18}H_{21}NO_4SNa$ $(M+Na)^+$ 370.1089, found 370.1087.

(3*S*,3a*R*,5*S*,6a*R*)-3-Allyl-2-(4-methoxybenzyl)-3a,5-divinylhexahydrofuro[2,3-*d*]isothiazole 1,1-dioxide [(±)-2.39]



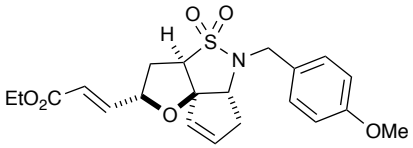
FTIR (neat): 1514, 1303, 1247, 1145 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 – 6.85 (m, 2H), 5.97 – 5.81 (m, 2H), 5.72 (dddd, *J* = 11.7, 9.5, 7.5, 6.4 Hz, 1H), 5.56 – 5.48 (m, 1H), 5.39 (ddd, *J* = 12.5, 4.3, 3.1 Hz, 2H), 5.27 – 5.20 (m, 1H), 5.00 – 4.92 (m, 2H), 4.76 (dd, *J* = 11.0, 5.9 Hz, 1H), 4.42 (d, *J* = 15.8 Hz, 1H), 4.10 (d, *J* = 15.8, 1H), 3.84 – 3.78 (s, 3H), 3.55 (d, *J* = 8.4 Hz, 1H), 3.38 (dd, *J* = 7.4, 5.2 Hz 1H), 2.75 (ddd, *J* = 13.6, 5.1, 0.9 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.34 – 2.26 (m, 1H), 2.02 (ddd, *J* = 13.6, 10.8, 8.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.5, 139.1, 136.8, 129.8, 118.1, 118.1, 117.1, 114.3, 88.5, 82.4, 66.9, 66.1, 55.7, 46.0, 35.1, 32.5;

HRMS calculated for $C_{20}H_{25}NO_4SNa$ $(M+Na)^+$ 398.1402, found 398.1401.

(*E*)-Ethyl 3-((2*S*,3a*R*,5a*R*,8a*R*)-5-(4-methoxybenzyl)-4,4-dioxido-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazol-2-yl)acrylate [(±)-2.40]



According to general procedure **A**, **2.37** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), ethyl acrylate (3.0 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.40** (61 mg, 0.147 mmol, 49%) as a yellow oil.

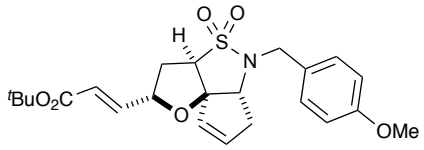
FTIR (neat): 1718, 1514, 1303, 1149 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.28 – 7.24 (m, 2H), 6.90 – 6.82 (m, 3H), 6.01 (ddd, *J* = 9.7, 7.9, 1.9 Hz, 2H), 5.71 (dt, *J* = 2.2, 5.7 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.04 (d, *J* = 14.4 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.59 (dd, *J* = 7.2, 3.7 Hz, 1H), 2.63 – 2.44 (m, 3H), 2.14 (dt, *J* = 13.8, 9.9 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.9, 159.5, 144.1, 135.4, 130.2 130.1, 126.7, 122.2, 114.2, 97.8, 76.8, 64.6, 63.6, 60.7, 55.3, 45.5, 35.3, 35.2, 14.2;

HRMS calculated for $C_{21}H_{25}NO_6SNa$ $(M+Na)^+$ 442.1300, found 442.1283.

(*E*)-*tert*-Butyl 3-((2*S*,3a*R*,5a*R*,8a*R*)-5-(4-methoxybenzyl)-4,4-dioxido-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazol-2-yl)acrylate [(±)-2.41]



According to general procedure **A**, **2.37** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), *t*-butyl acrylate (4.3 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **2.41** (69 mg, 0.156 mmol, 52%) as a yellow oil.

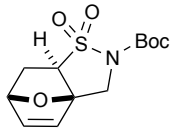
FTIR (neat): 2978, 1710, 1514, 1308, 1151 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.27 – 7.23 (m, 2H), 6.90 – 6.85 (m, 2H), 6.74 (dd, *J* = 15.7, 5.3 Hz, 1H), 6.01 – 5.98 (m, 1H), 5.94 (dd, *J* = 15.7, 1.4 Hz, 1H), 5.71 (dt, *J* = 5.7, 2.2 Hz, 1H), 4.59 (dd, *J* = 7.3, 2.7 Hz, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.03 (d, *J* = 14.4 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, *J* = 19.7, 1.9 Hz, 1H), 3.57 (dd, *J* = 7.2, 3.8 Hz, 1H), 2.80 (ddd, *J* = 13.8, 5.8, 2.0 Hz, 1H), 2.60 – 2.46 (m, 1H), 2.13 (dt, *J* = 13.8, 9.9 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.46 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.2, 159.5, 142.9, 135.4, 130.2, 130.1, 126.7, 124.1, 114.2, 97.7, 80.8, 76.8, 64.6, 63.6, 55.3, 45.4, 35.2, 35.2, 28.1;

HRMS calculated for $C_{23}H_{29}NO_6SNa$ $(M+Na)^+$ 470.1613, found 470.1601.

(3a*R*,6*S*,7a*R*)-*tert*-Butyl 3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole-2-carboxylate 1,1-dioxide [(±)-2.42]



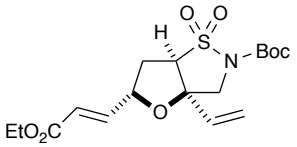
Mp 129 ºC;

FTIR (neat): 2981, 2935, 1720, 1458, 1334, 1137 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.40 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.11 (t, *J* = 5.2 Hz, 1H), 5.04 (dd, *J* = 4.6, 1.7 Hz, 1H), 4.12 – 3.98 (m, 2H), 3.14 (dd, *J* = 7.8, 3.1 Hz, 1H), 2.50 (ddd, *J* = 12.5, 4.6, 3.2 Hz, 1H), 1.65 (dd, *J* = 12.5, 7.8 Hz, 1H), 1.32 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 140.6, 132.8, 88.2, 84.4, 79.6, 62.3, 47.1, 30.2, 28.1; HRMS calculated for $C_{12}H_{17}NO_5SNa$ $(M+Na)^+$ 310.0725, found 310.0720.

(3a*R*,6a*R*)-*tert*-Butyl 5-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-3a-vinyltetrahydrofuro[2,3-d]isothiazole-2(5*H*)-carboxylate 1,1-dioxide [(±)-2.43]



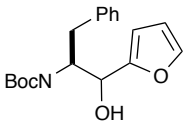
FTIR (neat): 2982, 2935, 1724, 1514, 1313, 1134 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.86 (dd, *J* = 15.6, 6.0 Hz, 1H), 6.12 – 6.05 (m, 1H), 5.97 – 5.89 (m, 1H), 5.60 (dd, *J* = 17.0, 0.6 Hz, 1H), 5.38 (ddd, *J* = 10.6, 4.6, 0.6 Hz, 1H), 5.02 – 4.94 (m, 1H), 4.25 – 4.17 (m, 2H), 4.01 – 3.94 (m, 1H), 3.78 (t, *J* = 6.6 Hz, 1H), 3.70 – 3.64 (m, 1H), 2.87 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.54 (d, *J* = 2.6 Hz, 10H), 1.32 – 1.27 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.9, 149.5, 144.6, 136.1, 122.8, 118.4, 85.2, 85.0, 79.5, 68.5, 60.8, 53.1, 34.1, 28.0, 14.2;

HRMS calculated for $C_{17}H_{25}NO_7SNa$ $(M+Na)^+$ 410.1249, found 410.1243.

***tert*-Butyl (2*S*)-1-(furan-2-yl)-1-hydroxy-3-phenylpropan-2-ylcarbamate (2.45)**



To a stirring suspension of imidazole (12.8 g, 188 mmol) in CH_2Cl_2 (40 mL) was added a solution of $PhOP(O)Cl_2$ (5.61 mL, 37.7 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h, the reaction was cooled to 0 °C and a solution of Boc-phenylalanine (10.0 g, 37.7 mmol) in CH_2Cl_2 (28 mL) was added and the reaction mixture stirred for 1 h. After such time, Weinreb amine (3.68 g, 37.7 mmol) was added and the reaction stirred at rt for 14 h. The reaction was quenched with citric acid (2 M aq., 80 mL), the organic layer washed with $NaHCO_3$ (1 M aq., 80 mL) and brine (80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to generate the desired intermediate as a clear oil (crude NMR analysis).

A portion of the crude (6.59 g, 25.3 mmol) in THF (84.5 mL) was cooled to -40 °C was stirred for 30 min. In a separate round bottom flask, a solution of furan (4.6 mL, 63.3 mmol) in THF (110 mL) was cooled to -78 °C to which ^{n}BuLi (26.3 mL) was added slowly and upon completion, was stirred for 30 min. After such time, this solution was added slowly to the crude mixture at -40 °C and the reaction mixture was subsequently stirred for an additional 6 h. After such time the reaction was quenched with NH_4Cl (sat. aq., 80 mL) and the reaction mixture warmed to rt. The aqueous layer was extracted with EtOAc (3 x 120 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired intermediate as a clear oil (crude NMR analysis). A portion of the crude

(1.0 g) in THF (12 mL)/MeOH (1.5 mL) was cooled to 0 °C and after stirring for 15 min, $NaBH_4$ (0.14 g, 3.8 mmol) was added and reaction stirred for 2 h at 0 °C. After such time the reaction was warmed to rt, diluted with EtOAc (10 mL) followed by HCl (10% aq., 10 mL). After stirring for 15 min, the organic layer was washed with HCl (10% aq., 10 mL), H_2O (10 mL), $NaHCO_3$ (sat. aq., 10 mL) and brine (10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the desired intermediate as a white solid.

Mp 144–146 °C;

FTIR (neat): 1716, 1454, 1292, 1172, 1132 cm^{-1};

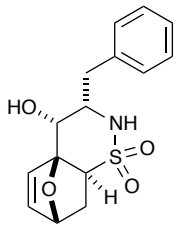
[Major Isomer] ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 – 7.43 (m, 1H), 7.34 – 7.17 (m, 5H), 6.38 – 6.29 (m, 2H), 4.80 (d, *J* = 19.2 Hz, 1H), 4.70 – 4.78 (m, 1H), 4.27 (br s, 1H), 3.55 (br s, 1H), 2.80 (d, *J* = 6.3 Hz, 2H), 1.35 (s, 9H);

[Minor Isomer] ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 (s, 1H), 7.16 – 7.35 (m, 5H), 6.43 – 6.38 (m, 2H), 4.89 (s, 1H), 4.75 (s, 1H), 4.14 (s, 1H), 3.08 (s, 1H), 2.88 – 2.99 (m, 2H), 1.41 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 156.6, 154.6, 154.0, 142.3, 142.0, 137.9, 137.6, 129.3, 129.3, 128.5, 128.5, 126.5, 126.5, 110.3, 107.8, 106.8, 80.0, 79.7, 77.3, 77.0, 76.7, 70.1, 68.7, 56.5, 55.4, 37.6, 36.6, 28.3;

HRMS calculated for $C_{18}H_{23}NO_4Na$ $(M+Na)^+$ 340.1525, found 340.1520.

(3*S*,4*R*,4a*S*,7*R*,8a*S*)-3-Benzyl-4-hydroxy-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazine 1,1-dioxide (2.47)



Carbamate **2.45** (2.0 g, 6.3 mmol) was dissolved in CH_2Cl_2 (32 mL), cooled to 0 °C and after stirring for 15 min TFA (1.95 mL, 25.2 mmol) was added cautiously. After stirring at rt for 3 h, the reaction was cooled to 0 °C and NaOH (10% aq., 35 mL) was added. The reaction was diluted with CH_2Cl_2 (32 mL), the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired carbamate intermediate as a white solid. The crude product (1.78 g) was dissolved in EtOH (40 mL) and NaOH (1 M aq., 40 mL) was added. After stirring at reflux for 14 h, the organic solvent was removed under reduced pressure. The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce the desired amino alcohol intermediate as a yellow oil. The crude material was dissolved in CH_2Cl_2 (11.7 mL), to which was added Et_3N (1.58 mL, 91 mmol) and the reaction was cooled to 0 ºC. After stirring for 10 min, 2-chloroethanesulfonyl chloride (0.52 mL, 4.89 mmol) was added drop wise over 5 min. The reaction mixture was warmed to rt and stirred for 12 h. After which time the crude mixture was concentrated and purified by flash

chromatography (1:2 hexane:EtOAc) to yield (1.0 g, 3.2 mmol, 52%) of **2.47** as a white solid.

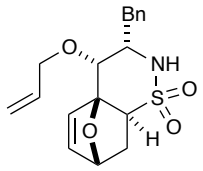
FTIR (neat): 3480, 3350, 2358, 1448, 1305, 1139 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 – 7.28 (m, 2H), 7.28 – 7.19 (m, 3H), 6.55 (dd, *J* = 5.7, 1.5 Hz, 1H), 6.34 (d, *J* = 5.7 Hz, 1H), 5.19 (dd, *J* = 4.7, 1.5 Hz, 1H), 4.64 (d, *J* = 10.6 Hz, 1H), 4.07 (dd, *J* = 16.4, 9.7 Hz 1H), 3.90 (s, 1H), 3.21 (dd, *J* = 7.9, 3.2 Hz 1H), 3.10 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.92 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.35 (s, 1H), 1.77 (dd, *J* = 12.2, 7.9 Hz 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.1, 136.1, 133.4, 129.1, 129.0, 127.2, 91.2, 79.5, 64.2, 56.2, 55.6, 37.0, 28.8;

HRMS calculated for $C_{15}H_{17}NO_4SNa$ $(M+Na)^+$ 330.0776, found 330.2017.

(3*S*,4*R*,4a*S*,7*R*,8a*S*)-4-(Allyloxy)-3-benzyl-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazine 1,1-dioxide (2.48)



Into a 1 dram vial was added **2.47** (85 mg, 0.27 mmol), DMF (0.6 mL, 0.46 M), Cs_2CO_3 (0.18 g, 0.55 mmol) and allyl bromide (25 μL, 0.30 mmol). The reaction was heated at 50 ºC and stirred for 4 h after which time the crude mixture was filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (1:2 hexane:EtOAc) to yield (86 mg, 2.48 mmol, 92%) of **2.48** as a yellow oil.

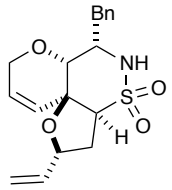
FTIR (neat): 3386, 3249, 2358, 1336, 1315, 1152 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.36 – 7.30 (m, 2H), 7.25 (dd, *J* = 7.2, 5.2 Hz 3H), 6.57 (dt, *J* = 5.6, 2.8 Hz 1H), 6.27 (d, *J* = 5.7, 1H), 6.04 – 5.94 (m, 1H), 5.33 (ddq, *J* = 20.2, 10.4, 1.4 Hz 2H), 5.21 (dd, *J* = 4.7, 1.6 Hz 1H), 4.71 (d, *J* = 12.1 Hz, 1H), 4.31 (dt, *J* = 5.5, 1.4 Hz, 2H), 4.14 (dddd, *J* = 12.1, 8.3, 7.1, 1.0 Hz, 1H), 3.64 (s, 1H), 3.20 (dd, *J* = 7.9, 3.3 Hz, 1H), 3.11 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.90 (dd, *J* = 14.3, 8.5 Hz, 1H), 2.60 (ddd, *J* = 12.2, 4.6, 3.4 Hz, 1H), 1.78 (dd, *J* = 12.1, 7.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.3, 136.5, 133.6, 133.4, 129.1, 129.0, 127.1, 118.2, 91.0, 79.5, 74.9, 72.5, 56.7, 56.1, 37.4, 29.0;

HRMS calculated for $C_{18}H_{21}NO_5SNa$ $(M+Na)^+$ 370.1089, found 370.1087.

(3a*S*,6*S*,6a*R*,10a*S*)-6-Benzyl-2-vinyl-3,3a,5,6,6a,8-hexahydro-2*H*-furo[2,3-*e*]pyrano[2,3-*d*][1,2]thiazine 4,4-dioxide (2.49)



According to general procedure **A**, sultam **2.48** (20 mg) underwent ROM-RCM-CM with ethylene to yield **2.49** (18 mg, 90%) as a clear oil.

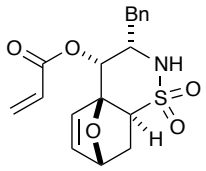
FTIR (neat): 3481, 2975, 1724 1445, 1308, 1139 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 – 7.17 (m, 3H), 7.14 (ddd, *J* = 9.5, 6.6, 3.4 Hz, 2H), 6.46 (d, *J* = 5.7 Hz, 1H), 6.37 (dd, *J* = 5.7, 1.6 Hz, 1H), 5.75 (dddd, *J* = 17.2, 10.0, 7.6, 5.7 Hz, 1H), 5.16 (ddd, *J* = 13.6, 11.0, 1.1 Hz, 2H), 5.02 (dd, *J* = 4.6, 1.6 Hz, 1H), 4.03 – 3.90 (m, 3H), 3.80 – 3.70 (m, 2H), 3.25 – 3.16 (m, 2H), 3.01 (dd, *J* = 13.4, 5.1 Hz 1H), 2.18 (dt, *J* = 12.7, 4.4 Hz, 1H), 1.87 (dd, *J* = 12.7, 8.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 137.3, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8;

HRMS calculated for $C_{18}H_{21}NO_4SNa$ $(M+Na)^+$ 370.1089, found 370.1087.

(3*S*,4*R*,4a*S*,7*R*,8a*S*)-3-Benzyl-1,1-dioxido-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazin-4-yl acrylate (2.50)



To a stirring solution of sultam **2.47** (50 mg, 0.16 mmol), Et_3N (45 μL, 0.32 mmol), and CH_2Cl_2 (0.35 mL) in a 1 dram vial was added was added acryloyl chloride (17 μL, 0.21 mmol). After stirring for 4 h at rt, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to yield (53 mg, 0.14 mmol, 92%) of **2.50** as a yellow oil.

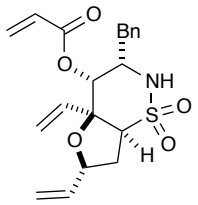
FTIR (neat): 3470, 2980, 1726 1452, 1300, 1140 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 – 7.22 (m, 3H), 7.17 (dd, *J* = 6.6, 5.0 Hz, 2H), 6.62 (dd, *J* = 17.3, 1.0 Hz 1H), 6.54 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.27 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.06 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.95 (d, *J* = 5.8 Hz, 1H), 5.48 (d, *J* = 19.2 Hz, 1H), 5.22 (dd, *J* = 4.7, 1.6 Hz 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.21 (dtd, *J* = 11.6, 7.3, 1.0 Hz, 1H), 3.19 (dd, *J* = 7.9, 3.2 Hz, 1H), 2.84 (qd, *J* = 14.3, 7.3 Hz, 2H), 2.67 – 2.57 (m, 1H), 1.79 (dd, *J* = 12.2, 7.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 137.2, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8;

HRMS calculated for $C_{18}H_{19}NO_5SNa$ $(M+Na)^+$ 384.0882, found 384.0886.

(3*S*,4*R*,4a*S*,7a*S*)-3-Benzyl-1,1-dioxido-4a,6-divinylhexahydro-2*H*-furo[2,3-*e*][1,2]thiazin-4-yl acrylate (2.51)



According to general procedure **A**, sultam **2.50** (18 mg) underwent ROM-RCM-CM with ethylene to yield **2.51** (16 mg, 85%) as a clear oil.

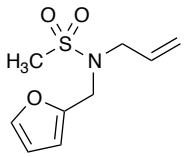
FTIR (neat): 3480, 2982, 1726 1448, 1305, 1139 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.23 (t, *J* = 7.3 Hz, 2H), 7.16 (dd, *J* = 15.3, 7.9 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 6.43 (dd, *J* = 17.2, 0.9 Hz, 1H), 6.08 (dd, *J* = 17.2, 10.4 Hz 1H), 5.91 (dd, *J* = 10.4, 0.9 Hz, 1H), 5.77 – 5.69 (m, 1H), 5.66 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 5.19 (dd, *J* = 13.9, 7.4 Hz, 2H), 5.09 (d, *J* = 10.2 Hz, 1H), 5.07 (s, 1H), 4.93 (dd, *J* = 16.2, 7.8 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.27 – 4.19 (m, 1H), 3.63 (d, *J* = 6.6 Hz, 1H), 2.73 – 2.60 (m, 3H), 2.03 (ddd, *J* = 14.0, 9.5, 6.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 164.2, 138.9, 138.3, 135.6, 133.2, 129.1, 128.7, 127.0, 127.0, 118.2, 118.1, 87.1, 81.4, 77.3, 61.8, 54.7, 37.5, 32.8;

HRMS calculated for $C_{20}H_{23}NO_5SNa$ $(M+Na)^+$ 412.1195, found 412.1190.

***N*-Allyl-*N*-(furan-2-ylmethyl)methanesulfonamide (2.52)**



Into a flame dried flask under argon was added methanesulfonyl chloride (2.03 mL, 26.2 mmol), Et_3N (4.4 mL, 31.6 mmol) and dry CH_2Cl_2 (70 mL). After cooling down to 0 ºC, furfurylamine (2.32 mL, 26.1 mmol) was added and the reaction flask stirred at room temperature for 5 h. After such time, the crude reaction mixture was washed with water and the organic layer dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield yellow oil. The crude material was subsequently dissolved in CH_3CN (100 mL), to which K_2CO_3 (7.27 g, 52.6 mmol) and allyl bromide (3.0 mL, 34.6 mmol) was added. After stirring at 60 ºC for 12 h, the crude reaction mixture was filtered through a pad of celite and washed with CH_2Cl_2. The crude mixture was concentrated under reduced pressure and purified by flash chromatography (4:1 hexane:EtOAc) to provide desired product **2.52** (5.35 g, 24.8 mmol, 95 % yield) as a yellow oil.

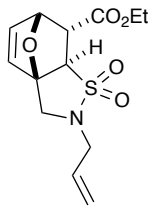
FTIR (neat): 2980,2934, 1733, 1504, 1328, 1147, 925 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.43 – 7.40 (m, 1H), 6.36 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 5.78 (ddt, *J* = 16.4, 10.1, 6.3 Hz, 1H), 5.30 (ddd, *J* = 10.9, 8.7, 1.3 Hz 2H), 4.42 (s, 2H), 3.82 (d, *J* = 6.2 Hz, 2H), 2.79 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.7, 142.9, 132.6, 119.4, 110.5, 110.0, 49.3, 42.5, 39.4;

HRMS calculated for $C_9H_{13}NO_3SNa$ $(M+Na)^+$ 238.051, found 238.0510.

(3a*R*,6*R*,7*R*,7a*R*)-Ethyl 2-allyl-3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole-7-carboxylate 1,1-dioxide [(±)-2.55]



To a flame dried flask was added, **2.52** (2 g, 9.29 mmol), diethyl chlorophosphate (1.6 mL, 11.1 mmol) and THF (40 mL). The reaction mixture was cooled to -78 ºC and after stirring for 15 mins, LHMDS (1.0 M solution in THF) was added. The resulting solution was warmed to 0 ºC and maintained for 2 h. To another flame dried flask, ethyl glyoxalate (3.7 mL, 18.7 mmol) and THF (40 mL) were added at -78 ºC. After stirring for 15 min, this solution was added to the anionic solution containing **2.52** via cannula. The resulting solution was stirred at -78 ºC for 7 h and then warmed to rt and stirred for an additional for 18 h. After such time, NH_4Cl (sat. aq., 25 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 25 mL). The organic layer was dried ($MgSO_4$), filtrated, concentrated under reduced pressure and purified by flash chromatography (7:1 hexane:EtOAc) to provide the mixture of Diels-Alder product **2.55** and precursor **2.54** product. Addition of hexane and Et_2O followed by cooling at 0 ºC, resulted in crystallization of the desired product **2.55** as a white solid (1.55g, 5.2 mmol, 56%).

FTIR (neat): 2983, 1736, 1301, 1141, 1020 cm^{-1};

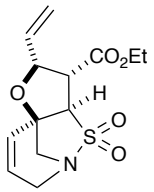
^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.51 (d, J = 5.7 Hz, 1H), 6.48 (dd, J = 5.7, 1.5 Hz, 1H), 5.88 (ddt, J = 16.6, 10.1, 6.4 Hz, 1H), 5.40 (dd, J = 4.7, 1.4 Hz 1H), 5.34

(dd, J = 17.1, 1.3 Hz, 1H), 5.29 (dd, J = 10.1, 1.0 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.84 (dd, J = 9.9, 5.9 Hz, 2H), 3.81 – 3.77 (m, 2H), 3.62 (d, J = 11.5 Hz, 1H), 3.55 (d, J = 3.7 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.8, 137.4, 135.6, 132.2, 119.9, 91.8, 81.0, 63.4, 61.8, 48.8, 48.3, 47.7, 14.2;

HRMS calculated for $C_{13}H_{17}NO_5SNa$ $(M+Na)^+$ 322.0725, found 322.0721.

(5a*R*,7*R*,8*R*,8a*R*)-Ethyl 7-vinyl-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine-8-carboxylate 1,1-dioxide [(±)-2.56]



To a flame dried flask was added dry CH_2Cl_2 (50 mL, 0.005 M), which was degassed with ethylene 30 min. After such time, sultam **2.55** (0.1 g, 0.33 mmol) and cat-**B** (0.03 g, 0.033 mmol) were added and the reaction was refluxed at 40 ºC for 1 h under ethylene (1 atm). After cooling to rt, the crude reaction mixture concentrated under reduced pressure and purified flash chromatography (6:1 hexane:EtOAc) to yield **2.56** (58 mg, 1.94 mmol, 59% yield) as a grey solid.

Mp 155 ºC;

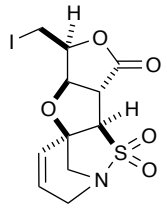
FTIR (neat): 2978, 1732, 1340, 1194, 999 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.34 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.73 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.58 (dt, *J* = 2.5, 10.1 Hz, 1H), 5.39 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.27 (dt, *J* = 10.4, 1.1 Hz 1H), 5.08 (dd, *J* = 8.2, 7.4 Hz, 1H), 4.21 (ddd, *J* = 6.7, 5.7, 1.9 Hz 1H), 4.18 – 4.12 (m, 3H), 3.82 – 3.75 (m, 2H), 3.57 (dd, *J* = 12.3, 2.0 Hz, 1H), 3.31 (dd, *J* = 12.3, 2.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.9, 134.3, 132.7, 124.1, 119.3, 87.2, 84.2, 72.2, 61.8, 52.7, 51.0, 50.9, 14.1;

HRMS calculated for $C_{13}H_{17}NO_5SNa$ $(M+Na)^+$ 322.0725, found 322.0716.

(5a*R*,6a*R*,7*S*,9a*R*,9b*R*)-7-(Iodomethyl)-6a,7,9a,9b-tetrahydro-2,5a-methanofuro[3',4':4,5]furo[2,3-*f*][1,2]thiazepin-9(3*H*)-one 1,1-dioxide [(±)-2.57]



Into a flame dried flask under argon sultam **2.56** (862 mg, 2.88 mmol), CH_3CN (11.5 mL, 0.25 M), and I_2 (730 mg, 2.88 mmol) were added. The resulting solution was stirred at rt for 24 h. The reaction was quenched with aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer was dried ($MgSO_4$) and was filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (6:1 hexane:EtOAc) to provide 78 mg (25%) of the desired compound.

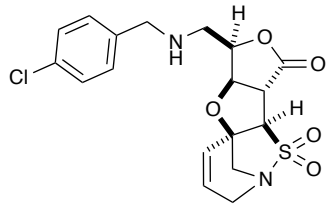
FTIR (neat): 2961, 1778, 1354, 1159, 1111 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.26 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.61 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.85 (d, *J* = 6.6 Hz, 1H), 4.66 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.24 (dt, *J* = 19.7, 2.5 Hz, 1H), 3.99 (dd, *J* = 6.6, 3.5 Hz, 1H), 3.87 – 3.82 (m, 2H), 3.59 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.43(dd, *J* = 11.1, 3.5 Hz, 1H), 3.30 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.29 (dd, *J* = 12.5, 1.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.5, 132.0, 125.0, 89.4, 85.0, 81.2, 73.1, 50.9, 50.9, 49.0, 3.6;

HRMS calculated for $C_{11}H_{12}INNaO_5S$ $(M+Na)^+$ 419.9379, found 419.9344.

(5a*R*,6a*R*,7*R*,9a*R*,9b*R*)-7-(((4-Chlorobenzyl)amino)methyl)-6a,7,9a,9b-tetrahydro-2,5a-methanofuro[3',4':4,5]furo[2,3-*f*][1,2]thiazepin-9(3*H*)-one 1,1-dioxide [(±)-2.58]



Into an oven dried flask under argon sultam **2.57** (50 mg, 0.13 mmol), 4-chlorobenzylamine (20 μL, 0.16 mmol), CH_3CN (2 mL), and K_2CO_3 (35 mg, 0.25 mmol) were added. The resulting solution was stirred at 65 ºC for 24 h. The reaction was filtered through Celite pad. The filtrate was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide 6 mg (12%) of the desired compound.

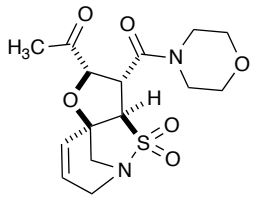
FTIR (neat): 3353, 2959, 2924, 1778, 1658, 1650, 1537, 1492, 1337, 1161, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.38 – 7.32 (m, 2H), 7.24 – 7.19 (m, 2H), 6.52 (t, *J* = 5.5 Hz, 1H), 6.44 (ddd, *J* = 10.1, 4.0, 2.0 Hz, 1H), 5.54 (dt, *J* = 10.2, 2.5 Hz, 1H), 5.01 (dd, *J* = 8.6, 0.9 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.34 (dd, *J* = 8.0, 3.0 Hz, 1H), 4.17 (dt, *J* = 19.4, 2.5 Hz, 1H), 3.88 – 3.83 (m, 1H), 3.77 (dt, *J* = 19.4, 2.2 Hz, 1H), 3.63 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.43 (qd, *J* = 12.4, 1.7 Hz, 2H), 3.27 (dq, *J* = 5.9, 2.8 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.4, 135.1, 134.9, 133.8, 129.1, 128.9, 123.3, 87.8, 87.0, 73.6, 72.5, 54.5, 50.9, 49.6, 43.6, 5.0;

HRMS calculated for $C_{18}H_{19}ClN_2NaO_5S$ $(M+Na)^+$ 433.0601; found 433.0598.

1-((5a*R*,7*S*,8*R*,8a*R*)-8-(Morpholine-4-carbonyl)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)ethanone [(±)-2.59]



Into an oven-dried flask under argon sultam **2.57** (35 mg, 0.09 mmol), morpholine (10 μl, 0.11 mmol), CH_3CN (2 mL), and K_2CO_3 (24 mg, 0.17 mmol) were added. The resulting solution was stirred at 65 ºC for 18 h. The reaction was filtered through Celite pad. The filtrate was concentrated under reduced pressure and purified by flash chromatography (EtOAc) to provide 11 mg (38%) of the desired compound.

FTIR (neat): 3353, 2959, 2924, 1725, 1685, 1537, 1492, 1337, 1161, 1110, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.44 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.64 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.73 (d, *J* = 9.0 Hz, 1H), 4.24 (dd, *J* = 9.0, 5.6, 2.7 Hz, 1H), 4.23 (dt, *J* = 19.4, 2.5 Hz, 1H), 4.02 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.84 (dt, *J* = 19.5, 2.2 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.72 – 3.66 (m, 3H), 3.64 – 3.51 (m, 5H), 3.35 (dd, *J* = 12.4, 2.0 Hz, 1H), 2.32 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 207.6, 167.6, 133.2, 124.4, 88.1, 86.4, 73.7, 66.6, 66.4, 51.7, 51.0, 47.9, 46.7, 42.7, 27.5;

HRMS calculated for $C_{15}H_{20}N_2O_6SNa$ $(M+Na)^+$ 379.0940, found 379.0930.

5.3 Experimental Data for Chapter 3

General procedure A: Aza-Michael reaction

Into a 1-dram vial was added a solution of dihydroisothiazole 1,1-dioxide in dry MeOH (1 M), DBU (10 mol %) and amine (1.5 eq). The vial was placed in oil bath and heated at 60 ºC for 12 h. After such time the reaction was diluted in CH_2Cl_2:MeOH (9:1), purified by column chromatography (1:2 hexane:EtOAc) to yield the desired product.

General procedure B: Alkylation/arylation reaction

Into an r. b. flask was added sulfonamide (1 eq) in dry CH_2Cl_2 (0.1 M), Cs_2CO_3 (1.3 eq) and alkyl bromide (aryl bromide) (1.3 eq). The resulting mixture was stirrer at 60 ºC in oil bath for 12 h. The reaction was filtered through Celite plug, concentrated and purified by column chromatography (1:1 hexane:EtOAc) to yield the desired sultam product.

General procedure C: Carbonylation reaction

Into an r. b. flask was added sulfonamide (1 eq) in dry CH_3CN (0.1 M). DMAP (0.1 eq), acyl chloride (1.1 eq) and Et_3N (1.3 eq) were added at 0 ºC. The resulting mixture was stirrer at rt for 1 h. The reaction was quenched with water, the solution extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Flash chromatography (2:1 hexane:EtOAc) afforded the desired product.

General procedure D: Sulfonylation followed by allylation to yield 3.61a–h:

An r. b. flask was containing amine (7 mmol, 1 eq) in dry CH_2Cl_2 (0.5 M) was cooled to 0º C and the reaction mixture was stirred for 10 min. After such time, 2-chloroethanesulfonyl chloride (7 mmol, 1 eq) and the reaction mixture was warmed to rt and stirred for 2 h. The crude reaction mixture was quenched with 10% HCl. aq, the organic layer separated and washed with water, brine, dried over $MgSO_4$. Simple filtration and subsequent concentration yielded the desire sulfonamide in excellent crude purity. The crude was taken forward where was solvated in dry CH_3CN (0.2 M), followed by addition of K_2CO_3 (21 mmol, 3 eq) and allyl bromide (10.5 mmol, 1.5 eq). The reaction mixture was heated at 60 ºC for 2–4 h (TLC monitoring), filtered through a Celite plug, concentrated and purified by column chromatography (3:1 hexane:EtOAc) to yield the desired sulfonamides **3.61a**–**h**.

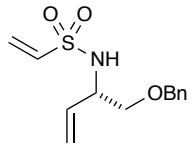
General procedure E: RCM of vinylsulfonamide to yield dihydroisothiazole 1,1-dioxide 3.62–3.69:

Into an r. b. flask fitted with reflux condenser was added vinylsulfonamide **3.61a**–**h** (9.0 mmol, 1 eq), cat-**B** (8 mol%), and Ar degassed DCE (0.02 M). The reaction was heated at 45 ºC for 1–2 h (TLC monitoring) under Ar atmosphere. After such time, the reaction was cooled to rt, quenched with ethyl vinyl ether (EVE) [0.5 ml) and after stirring for an additional 10 min, the crude mixture was concentrated and purified by flash chromatography (7:3 hexane:EtOAc) to yield the desired dihydroisothiazole 1,1-dioxide **3.61a**–**h**.

General procedure F: Aza-Michael Library protocol:

Into a 1-dram vial was added a solution of dihydroisothiazole 1,1-dioxide (*R*)- and (*S*)-**3.33** as well as **3.62– 3.69** (75 mg, 1 eq) in dry MeOH (1 M), DBU (10 mol %) and amine (1.5 eq). The vial was placed on a reaction block and heated at 60 ºC for 12 h. After such time the reaction was diluted in CH_2Cl_2:MeOH (9:1), filtered through a silica SPE (vacuum box) and flushed with CH_2Cl_2:MeOH (9:1) [10 ml]. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

(*S*)-*N*-(1-(benzyloxy)but-3-en-2-yl)ethenesulfonamide



To a solution of amine (0.809 g, 4.56 mmol), DMAP (56 mg, 0.458 mmol) and CH_2Cl_2 (15 mL) were added. 1,2-dichloroethanesulfonyl chloride (0.53 mL, 5.07 mmol) and Et_3N (1.6 mL, 11.48 mmol) was added slowly. The resulting solution was stirred at rt for overnight. The organic layer was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 6:1 Hexane/EtOAc) afforded 0.60 g (50%) of desired product as yellow oil.

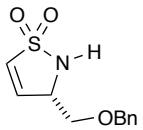
IR (neat): 3282, 1328, 1147, 1110, 736 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.41 – 7.29 (m, 5H), 6.49 (dd, *J* = 16.5, 9.9 Hz 1H), 6.22 (d, *J* = 16.5 Hz, 1H), 5.90 – 5.77 (m, 2H), 5.32 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.24 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.76 (d, *J* = 7.3, 1H), 4.59 – 4.48 (m, 2H), 4.09 – 3.99 (m, 1H), 3.63 – 3.45 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.4, 136.9, 135.3, 128.1, 128.0, 127.8, 126.0, 117.7, 73.4, 72.1, 55.9;

HRMS calculated for $C_{13}H_{17}NO_3SNa$ $(M+Na)^+$ 290.0827, found 290.0816.

(*S*)-3-((Benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide [(*S*)-3.3]



To a solution of diene sulfonamide (1.54 g, 5.746 mmol) in degassed 1,2-chloroethane (350 mL, 0.016 M) was added Grubbs 2nd-generation catalyst (487 mg, 0.574 mmol) in one portion and the reaction was refluxed for 6 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 3:1 Hexane/EtOAc) afforded 1.20 g (88 % yield) of sultam as brownish liquid.

$[\alpha]_D^{25}$ = +68.83 (*c* = 3.10, CH_2Cl_2);

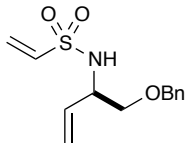
IR (neat): 3259, 3087, 2864, 1286, 1157, 1105 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.30 (m, 5H), 6.80 (dd, *J* = 6.5, 1.8 Hz, 1H), 6.77 (dd, *J* = 6.6, 1.9 Hz, 1H), 4.69 (s, 1H), 4.62 – 4.53 (m, 2H), 4.45 (dt, *J* = 6.4, 4.9 Hz, 1H), 3.61 (qd, *J* = 9.6, 5.9 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 136.6, 128.7, 128.3, 127.9, 127.5, 73.2, 70.2, 58.6;

HRMS calculated for $C_{13}H_{17}NO_3SNa$ $(M+Na)^+$ 262.0514, found 290.0515.

(*R*)-*N*-(1-(Benzyloxy)but-3-en-2-yl)ethenesulfonamide



Yield 46%;

$[\alpha]_D^{25}$ = +20.40 (*c* = 2.10, CH_2Cl_2);

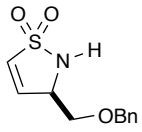
IR (neat): 3280, 1328, 1145, 1110, 968, 736 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.27 (m, 2H), 7.27 – 7.21 (m, 3H), 6.41 (dd, *J* = 20.0, 10.4 Hz, 1H), 6.14 (d, *J* = 16.5 Hz, 1H), 5.78 (d, *J* = 5.0 Hz, 1H), 5.75 (ddd, *J* = 16.5, 10.4, 5.0 Hz, 1H), 5.24 (dt, *J* = 15.0, 1.1 Hz, 1H), 5.16 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.68 (d, *J* = 7.1 Hz, 1H), 4.46 (dd, *J* = 15.5, 11.9 Hz, 2H), 4.00 – 3.92 (m, 1H), 3.52 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.44 – 3.38 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.4, 136.9, 135.3, 128.6, 128.0, 127.8, 126.0, 117.7, 73.4, 72.1, 55.9;

HRMS calculated for $C_{13}H_{17}NO_3SNa$ $(M+Na)^+$ 290.0827, found 290.0823.

(*R*)-3-((Benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide [(*R*)-3.3]



Yield 92%;

$[\alpha]_D^{25} = -68.83$ ($c = 3.10$, CH_2Cl_2);

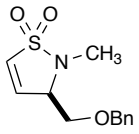
IR (neat): 3255, 2862, 1315, 1279, 1160, 1103 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.30 (m, 5H), 6.80 (dd, J = 6.5, 1.8 Hz, 1H), 6.77 (dd, J = 6.6, 1.9 Hz, 1H), 4.67 (s, 1H) 4.57 (dd, J = 14.4, 12.0 Hz, 2H), 4.47 – 4.42 (m, 1H), 3.61 (ddd, J = 16.1, 9.6, 5.9 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.2, 136.9, 129.1, 128.7, 128.2, 127.9, 73.6, 70.5, 58.9;

HRMS calculated for $C_{13}H_{17}NO_3SNa$ $(M+Na)^+$ 262.0514, found 290.0510.

(*R*)-3-((Benzyloxy)methyl)-2-methyl-2,3-dihydroisothiazole 1,1-dioxide (3.4)



Procedure B; Yield 79%;

$[\alpha]_D^{25}$ = +38.03 (*c* = 1.27, CH_2Cl_2);

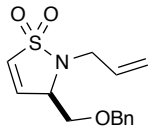
IR (neat): 3205, 3085, 2927, 2864, 1608, 1454, 1290, 1153, 1097 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 – 7.30 (m, 5H), 6.85 (dd, *J* = 7.0, 2.0 Hz, 1H), 6.71 (dd, *J* = 7.0, 2.1 Hz, 1H), 4.62 – 4.51 (m, 2H), 4.05 (tt, *J* = 6.1, 2.1 Hz, 1H), 3.69 (dd, *J* = 9.5, 6.1 Hz, 1H), 3.55 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.88 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.1, 137.0, 128.5, 128.0, 127.7, 127.5, 73.6, 70.4, 64.3, 29.8;

HRMS calculated for $C_{12}H_{15}NO_3SNa$ $(M+Na)^+$ 276.0670, found 276.0663.

(*R*)-2-Allyl-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.5)



Procedure B; Yield 87%;

$[\alpha]_D^{25}$ = +31.57 (*c* = 0.70, CH_2Cl_2);

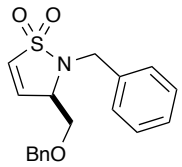
IR (neat): 3086, 2901, 2864, 1610, 1363, 1294, 1153, 1105, 738 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.35 (m, 2H), 7.33 (td, *J* = 6.4, 1.4 Hz, 3H), 6.89 (dd, *J* = 6.9, 2.2 Hz, 1H), 6.71 (dd, *J* = 6.9, 2.0 Hz, 1H), 5.91 (dddd, *J* = 17.2, 10.1, 7.2, 5.8 Hz, 1H), 5.30 (ddd, *J* = 17.1, 2.8, 1.4 Hz, 1H), 5.26 (ddd, *J* = 10.1, 2.4, 1.1 Hz, 1H), 4.55 (s, 2H), 4.21 (ddt, *J* = 6.9, 5.7, 2.1 Hz, 1H), 3.94 – 3.83 (m, 2H), 3.70 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.50 (dd, *J* = 9.4, 6.8 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 137.2, 132.6, 128.6, 128.1, 127.7, 127.5, 120.0, 73.6, 70.5, 61.8, 46.8;

HRMS calculated for $C_{14}H_{17}NO_3SNa$ $(M+Na)^+$ 302.0827, found 302.0820.

(*R*)-2-Benzyl-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.6)



Procedure B; Yield 98%;

$[\alpha]_D^{25}$ = +42.13 (*c* = 2.15, CH_2Cl_2);

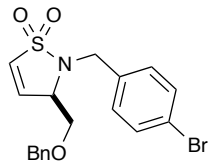
IR (neat): 3087, 2862, 1609, 1497, 1454, 1288, 1153, 1107, 738, 698 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 – 7.29 (m, 8H), 7.26 – 7.22 (m, 2H), 6.87 (dd, *J* = 7.0, 2.3 Hz, 1H), 6.75 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.47 (d, *J* = 15.3 Hz, 1H), 4.40 (s, 2H), 4.38 (d, *J* = 13.7 Hz, 1H), 4.10 (ddt, *J* = 7.5, 5.3, 2.1 Hz, 1H), 3.46 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.36 (dd, *J* = 9.5, 6.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 137.2, 135.6, 128.8, 128.7, 128.6, 128.5, 128.0, 127.8, 127.3, 73.5, 70.1, 62.0, 47.2;

HRMS calculated for $C_{18}H_{19}NO_3SNa$ $(M+Na)^+$ 352.0983, found 352.0974.

(*R*)-3-((Benzyloxy)methyl)-2-(4-bromobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.7)



Procedure B; Yield 71%;

$[\alpha]_D^{25}$ = +32.00 (*c* = 1.50, CH_2Cl_2);

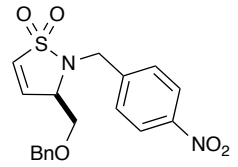
IR (neat): 3263, 2860, 1452, 1286, 1153, 1103, 746 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.30 (m, 4H), 7.24 (d, *J* = 8.5 Hz, 4H), 6.84 (dd, *J* = 7.0, 2.2 Hz, 1H), 6.75 (dd, *J* = 7.0, 1.9 Hz, 1H), 4.44 (d, *J* = 14.0 Hz, 1H), 4.42 (s, 2H), 4.33 (d, *J* = 15.5 Hz, 1H), 4.09 (tt, *J* = 6.0, 2.4 Hz, 1H), 3.47 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.40 (dd, *J* = 9.5, 6.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.0, 136.9, 134.8, 131.8, 130.3, 128.6, 128.1, 127.8, 127.4, 122.0, 73.6, 70.3, 62.2, 46.7;

HRMS calculated for $C_{18}H_{18}BrNO_3SNa$ $(M+Na)^+$ 430.0088, found 430.0085.

(*R*)-3-((Benzyloxy)methyl)-2-(4-nitrobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.8)



Procedure B; Yield 36%;

$[\alpha]_D^{25}$ = +80.00 (*c* = 0.50, CH_2Cl_2);

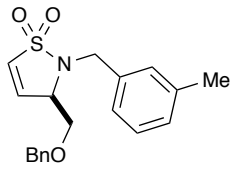
IR (neat): 3082, 2864, 1609, 1518, 1346, 1288, 1153, 748 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 5.1, 1.6 Hz, 3H), 7.23 – 7.17 (m, 2H), 6.84 (dd, *J* = 7.0, 1.9 Hz, 1H), 6.79 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.66 (d, *J* = 16.1 Hz, 1H), 4.44 (d, *J* = 16.0 Hz, 1H), 4.41 (d, *J* = 1.9 Hz, 2H), 4.16 (t, *J* = 5.8 Hz, 1H), 3.49 (d, *J* = 5.6 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.6, 143.7, 136.7, 136.5, 129.1, 128.6, 128.3, 127.9, 127.6, 123.8, 73.6, 70.7, 63.1, 47.0;

HRMS calculated for $C_{18}H_{18}N_2O_5SNa$ $(M+Na)^+$ 397.0834, found 397.0836.

(*R*)-3-((Benzyloxy)methyl)-2-(3-methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.9)



Procedure B; Yield 47%;

$[\alpha]_D^{25}$ = +54.29 (*c* = 1.05, CH_2Cl_2);

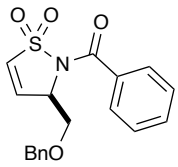
IR (neat): 3088, 2920, 2864, 1285, 1155, 1105, 1094, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.38 – 7.30 (m, 3H), 7.24 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 7.0, 2.3 Hz, 1H), 6.75 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 4.40 (s, 2H), 4.35 (d, *J* = 15.2 Hz, 1H), 4.10 (ddt, *J* = 7.4, 5.2, 2.1 Hz, 1H), 3.46 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.35 (dd, *J* = 9.5, 6.7 Hz, 1H), 2.33 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.4, 137.4, 137.2, 135.5, 129.3, 128.8, 128.6, 128.5, 128.0, 127.8, 127.2, 125.7, 73.5, 70.0, 61.9, 47.1, 21.4;

HRMS calculated for $C_{19}H_{21}NO_3SNa$ $(M+Na)^+$ 366.1140, found 366.1139.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(phenyl)methanone (3.10)



Procedure C; Yield 74%;

$[\alpha]_D^{25}$ = +247.64 (*c* = 0.55, CH_2Cl_2);

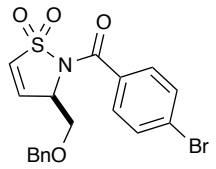
IR (neat): 3088, 2864, 1678, 1448, 1330, 1278, 1166, 1114, 723, 696 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.88 (dt, *J* = 8.4, 1.5 Hz, 2H), 7.64 61 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 7.04 (dd, *J* = 7.1, 2.8 Hz, 1H), 6.68 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.52 (ddd, *J* = 9.0, 4.6, 2.7 Hz, 1H), 4.66 – 4.58 (m, 2H), 3.91 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.70 (dd, *J* = 9.7, 6.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.2, 137.3, 136.9, 133.9, 132.9, 128.6, 128.6, 128.4, 128.0, 127.7, 126.5, 73.7, 69.2, 59.7;

HRMS calculated for $C_{18}H_{17}NO_4SNa$ $(M+Na)^+$ 366.0776, found 366.0765.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-bromophenyl)methanone (3.11)



Procedure C; Yield 18%;

$[\alpha]_D^{25}$ = +182.66 (*c* = 3.13, CH_2Cl_2);

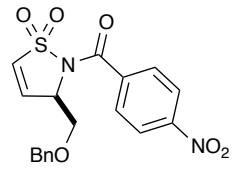
IR (neat): 30888, 2864, 1681, 1589, 1331, 1167, 1111, 1012, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 – 7.72 (m, 2H), 7.66 – 7.62 (m, 2H), 7.39 – 7.29 (m, 5H), 7.04 (dd, *J* = 7.1, 2.8 Hz, 1H), 6.68 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.50 (ddd, *J* = 6.4, 4.3, 2.6 Hz, 1H), 4.61 (s, 2H), 3.89 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.68 (dd, *J* = 9.7, 6.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 167.3, 137.2, 137.0, 132.7, 131.8, 130.2, 128.6, 128.1, 128.0, 127.7, 126.4, 73.7, 69.0, 59.7;

HRMS calculated for $C_{18}H_{16}BrNO_4SNa$ $(M+Na)^+$ 443.9881, found 443.9879.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-nitrophenyl)methanone (3.12)



Procedure C; Yield 75%;

$[\alpha]_D^{25}$ = +189.46 (*c* = 3.96, CH_2Cl_2);

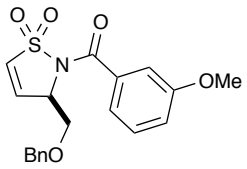
IR (neat): 3086, 2866, 1684, 1525, 1335, 1315, 1169, 1124, 1111, 734 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.37 – 8.32 (m, 2H), 8.01 – 7.96 (m, 2H), 7.41 – 7.30 (m, 5H), 7.06 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.71 (dd, *J* = 7.2, 2.0 Hz, 1H), 5.47 (dddd, *J* = 8.9, 4.1, 2.7, 2.1 Hz, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.93 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.74 (dd, *J* = 9.7, 6.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.3, 150.1, 139.2, 137.2, 137.1, 129.7, 128.6, 128.2, 127.7, 126.4, 123.6, 73.7, 68.7, 59.8;

HRMS calculated for $C_{18}H_{16}N_2O_6SNa$ $(M+Na)^+$ 411.0627, found 411.0621.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(3-methoxyphenyl)methanone (3.13)



Procedure C; Yield 54%;

$[\alpha]_D^{25}$ = +214.73 (*c* = 1.60, CH_2Cl_2);

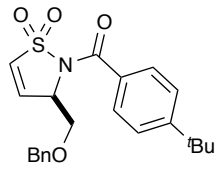
IR (neat): 3086, 2866, 1682, 1583, 1328, 1159, 1114, 1041, 746 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.49 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.44 – 7.34 (m, 6H), 7.34 – 7.28 (m, 1H), 7.15 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 7.03 (dd, *J* = 7.1, 2.8 Hz, 1H), 6.67 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.52 (ddd, *J* = 9.0, 4.3, 2.6 Hz, 1H), 4.62 (d, *J* = 1.5 Hz, 2H), 3.90 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.87 (s, 3H), 3.69 (dd, *J* = 9.7, 6.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.0, 159.4, 137.3, 136.9, 135.0, 129.5, 128.5, 128.0, 127.7, 126.5, 121.1, 119.7, 113.1, 73.7, 69.2, 59.7, 55.4;

HRMS calculated for $C_{19}H_{19}NO_5SNa$ $(M+Na)^+$ 396.0882, found 396.0873.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-(*tert*-butyl)phenyl)methanone (3.14)



Procedure C; Yield 58%;

$[\alpha]_D^{25}$ = +211.92 (*c* = 1.09, CH_2Cl_2);

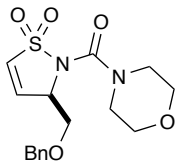
IR (neat): 3090, 2962, 2868, 1680, 1606, 1332, 1278, 1168, 1116, 736 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.88 – 7.84 (m, 2H), 7.54 – 7.49 (m, 2H), 7.39 – 7.34 (m, 4H), 7.31 (m, 1H), 7.03 (dd, *J* = 7.1, 2.7 Hz, 1H), 6.67 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.55 (ddd, *J* = 9.0, 4.3, 2.6 Hz, 1H), 4.61 (d, *J* = 4.2 Hz, 2H), 3.89 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.67 (dd, *J* = 9.7, 6.6 Hz, 1H), 1.36 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.1, 156.6, 137.3, 136.9, 131.0, 128.7, 128.5, 128.0, 127.7, 126.5, 125.5, 73.7, 69.3, 59.7, 35.1, 31.1;

HRMS calculated for $C_{22}H_{25}NO_4SNa$ $(M+Na)^+$ 422.1402, found 422.1401.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(morpholino)methanone (3.15)



Procedure C; Yield 98%;

$[\alpha]_D^{25}$ = +83.10 (*c* = 3.39, CH_2Cl_2);

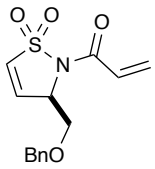
IR (neat): 3086, 2964, 2924, 2860, 1682, 1614, 1427, 1317, 1244, 1159, 1115, 740 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 – 7.34 (m, 2H), 7.34 – 7.29 (m, 3H), 6.93 (dd, *J* = 6.8, 2.6 Hz, 1H), 6.64 (dd, *J* = 6.8, 2.2 Hz, 1H), 5.54 – 5.49 (m, 1H), 4.56 (t, *J* = 3.6 Hz, 2H), 3.84 – 3.73 (m, 4H), 3.71 – 3.55 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 152.3, 137.5, 137.2, 128.5, 128.0, 127.6, 126.2, 73.3, 70.6, 66.5, 60.5, 46.8;

HRMS calculated for $C_{16}H_{20}N_2O_5SNa$ $(M+Na)^+$ 375.0991, found 375.0985.

(*R*)-1-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)prop-2-en-1-one (3.16)



Procedure C; Yield 86%;

$[\alpha]_D^{25}$ = +92.26 (*c* = 2.28, CH_2Cl_2);

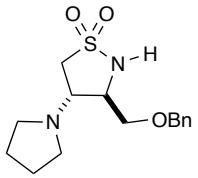
IR (neat): 2923, 2866, 1688, 1622, 1454, 1407, 1323, 1247, 1137, 1047, 977, 792, 738, 698 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.38 – 7.33 (m, 2H), 7.33 – 7.29 (m, 3H), 7.04 (dd, *J* = 7.2, 2.7 Hz, 1H), 6.95 (dd, *J* = 16.6, 10.4 Hz, 1H), 6.72 (dd, *J* = 7.2, 1.9 Hz, 1H), 6.58 (dd, *J* = 16.6, 1.4 Hz, 1H), 5.96 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.12 (dddd, *J* = 5.6, 3.6, 2.6, 2.0 Hz, 1H), 4.55 (s, 2H), 3.98 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.68 (dd, *J* = 9.6, 6.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.4, 137.7, 137.2, 132.2, 128.5, 128.0, 127.7, 127.5, 126.3, 73.7, 68.4, 59.5;

HRMS calculated for $C_{14}H_{15}NO_4SNa$ $(M+Na)^+$ 316.0620, found 316.0618.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.17)



Procedure A; Yield 88%; Mp 98 ºC;

$[\alpha]_D^{25} = -56.08$ (c = 5.27, CH_2Cl_2);

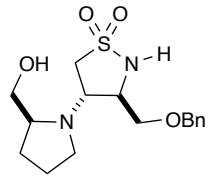
IR (neat): 3260, 2825, 1598, 1310, 1234, 1137, 1012 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm δ 7.41 – 7.35 (m, 2H), 7.35 – 7.30 (m, 3H), 4.71 (d, J = 7.5 Hz, 1H), 4.57 (s, 2H), 3.78 (dd, J = 7.7, 1.4 Hz, 1H), 3.71 (m, 2H), 3.65 – 3.56 (m, 1H), 3.22 (qd, J = 13.2, 8.0 Hz, 2H), 2.66 – 2.49 (m, 4H), 1.82 – 1.73 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 128.6, 128.1, 127.8, 73.5, 68.4, 61.8, 58.0, 49.8, 47.1, 23.5;

HRMS calculated for $C_{15}H_{22}N_2O_3SNa$ $(M+Na)^+$ 333.1249, found 333.1250.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*S*)-2-(hydroxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.18)



Procedure A; Yield 30%;

$[\alpha]_D^{25} = -62.37$ (*c* = 1.95, CH_2Cl_2);

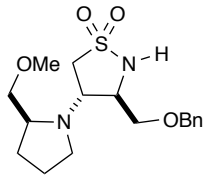
IR (neat): 3260, 2924, 1299, 1132, 1027 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 (ddd, *J* = 7.4, 4.4, 1.4 Hz, 2H), 7.26 (ddd, *J* = 12.7, 5.6, 4.1 Hz, 3H), 4.58 (s, 1H), 4.49 (dd, *J* = 11.9, 21.6 Hz, 2H), 3.89 (dt, *J* = 9.1, 7.2 Hz, 1H), 3.67 – 3.58 (m, 2H), 3.30 (ddd, *J* = 30.1, 10.9, 4.8 Hz, 2H), 3.13 (ddd, *J* = 37.9, 13.4, 7.0 Hz, 2H), 3.06 – 2.97 (m, 2H), 2.55 (dd, *J* = 15.9, 8.3 Hz, 1H), 1.82 – 1.57 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.1, 128.6, 128.2, 128.0, 73.5, 68.1, 65.0, 61.8, 59.5, 57.6, 52.5, 49.3, 29.1, 24.3;

HRMS calculated for $C_{16}H_{24}N_2O_4SNa$ $(M+Na)^+$ 363.1354, found 363.1349.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*S*)-2-(methoxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.19)



Procedure A; Yield 30%;

$[\alpha]_D^{25} = -83.43$ (c = 1.58, CH_2Cl_2);

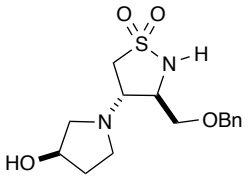
IR (neat): 3247, 2932, 2871, 1454, 1328, 1303, 1137, 1112 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 – 7.30 (m, 5H), 4.66 – 4.52 (m, 3H), 4.28 (dd, J = 16.4, 9.3 Hz, 1H), 3.74 (d, J = 3.5 Hz, 2H), 3.57 – 3.47 (m, 1H), 3.31 (s, 3H), 3.26 – 3.15 (m, 4H), 2.90 (ddd, J = 10.5, 6.2, 4.5 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.62 (dd, J = 16.7, 7.8 Hz, 1H), 1.88 – 1.69 (m, 3H), 1.55 – 1.46 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 128.6, 128.1, 127.8, 76.8, 73.6, 67.2, 61.5, 60.9, 59.1, 58.0, 46.1, 45.5, 28.4, 23.3;

HRMS calculated for $C_{17}H_{27}N_2O_4S$ $(M+H)^+$ 355.1692, found 355.1700.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*R*)-3-hydroxypyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.20)



Procedure A; Yield 72%;

$[\alpha]_D^{25} = -96.35$ (c = 3.43, CH_2Cl_2);

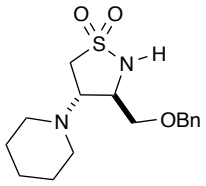
IR (neat): 3265, 2945, 2864, 1328, 1299, 1139, 1101, 700 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.36 (m, 2H), 7.35 – 7.30 (m, 3H), 4.82 (dd, J = 35.1, 7.8 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.34 (s, 1H), 3.81 (tt, J = 16.6, 8.3 Hz, 1H), 3.75 – 3.65 (m, 2H), 3.57 (dq, J = 12.2, 4.2 Hz, 1H), 3.29 (dd, J = 13.4, 6.5 Hz, 1H), 3.20 (dd, J = 13.3, 9.2 Hz, 1H), 2.82 (dd, J = 16.1, 7.5 Hz, 1H), 2.77 – 2.67 (m, 2H), 2.58 (m, 1H), 2.13 – 2.00 (m, 1H), 1.95 – 1.84 (m, 1H), 1.80 – 1.70 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.2, 128.6, 128.1, 127.9, 73.4, 70.8, 68.2, 68.0, 61.8, 61.7, 58.6, 57.8, 53.7, 48.1, 48.0, 47.5, 47.4, 34.3, 31.7, 29.2;

HRMS calculated for $C_{15}H_{22}N_2O_4SNa$ $(M+Na)^+$ 349.1198, found 349.1191.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(piperidin-1-yl)isothiazolidine 1,1-dioxide (3.21)



Procedure A; Yield 74%;

$[\alpha]_D^{25}$ = –95.66 (*c* = 4.27, CH_2Cl_2);

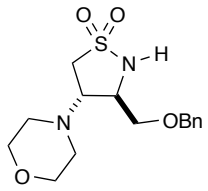
IR (neat): 3261, 2935, 2854, 1454, 1328, 1311, 1145, 1107, 912 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 – 7.29 (m, 5H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.58 – 4.55 (m, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 3.7 Hz, 2H), 3.68 – 3.57 (m, 1H), 3.57 – 3.50 (m, 1H), 3.30 (dd, *J* = 13.2, 7.2 Hz, 1H), 3.08 (dd, *J* = 13.2, 9.5 Hz, 1H), 2.50 (ddd, *J* = 10.6, 7.0, 3.5 Hz, 2H), 2.38 (ddd, *J* = 10.2, 6.1, 3.4 Hz, 2H), 1.62 – 1.48 (m, 5H), 1.44 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 128.6, 128.1, 127.9, 73.4 68.0 65.5, 56.6, 51.0, 45.0, 26.1, 24.3;

HRMS calculated for $C_{16}H_{24}N_2O_3SNa$ $(M+Na)^+$ 347.1405, found 347.1367.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-morpholinoisothiazolidine 1,1-dioxide (3.22)



Procedure A; Yield 44%;

$[\alpha]_D^{25} = -110.81$ (c = 2.84, CH_2Cl_2);

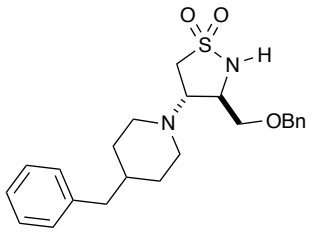
IR (neat): 3254, 2956, 2858, 1496, 1454,1336, 1296, 1134, 1117, 914 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 – 7.29 (m, 5H), 4.63 – 4.61 (m, 1H), 4.61 (dt, J = 11.9 Hz, 3H), 4.54 (d, J = 11.9 Hz, 1H), 3.73 (d, J = 3.3 Hz, 2H), 3.70 – 3.59 (m, 5H), 3.52 (ddd, J = 12.1, 8.4, 3.6 Hz, 1H), 3.31 (dd, J = 13.4, 6.7 Hz, 1H), 3.11 (dd, J = 13.4, 9.7 Hz, 1H), 2.55 (ddd, J = 10.9, 5.7, 3.3 Hz, 2H), 2.46 (ddd, J = 11.1, 5.2, 3.8 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.1, 128.6, 128.2, 128.0, 73.4, 67.5, 66.8, 65.0, 56.1, 50.0, 45.2;

HRMS calculated for $C_{15}H_{22}N_2O_4SNa$ $(M+Na)^+$ 349.1198, found 349.1198.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(4-benzylpiperidin-1-yl)isothiazolidine 1,1-dioxide (3.23)



Procedure A; Yield 35%;

$[\alpha]_D^{25}$ = –81.83 (*c* = 2.80, CH_2Cl_2);

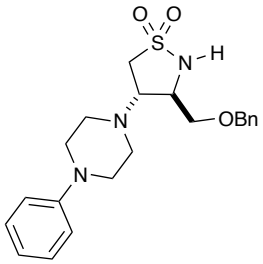
IR (neat): 3263, 3026, 2918, 2850, 1452, 1330, 1303, 1151, 1130 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 – 7.34 (m, 3H), 7.34 – 7.28 (m, 4H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 2H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.58 – 4.56 (m, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 3.70 (d, *J* = 3.7 Hz, 2H), 3.64 (dd, *J* = 16.5, 8.9 Hz, 1H), 3.56 – 3.47 (m, 1H), 3.26 (dd, *J* = 13.2, 7.2 Hz, 1H), 3.07 (dd, *J* = 13.2, 9.5 Hz, 1H), 2.80 – 2.72 (m, 2H), 2.58 – 2.46 (m, 2H), 2.20 (td, *J* = 11.4, 2.5 Hz, 1H), 2.04 (td, *J* = 11.4, 9.1 Hz, 1H), 1.69 – 1.60 (m, 2H), 1.51 (ddd, *J* = 11.3, 7.5, 3.9 Hz, 1H), 1.31 – 1.11 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.3, 137.3, 129.0, 128.6, 128.2, 128.1, 127.8, 125.9, 73.4, 68.0, 65.0, 56.7, 53.9, 46.7, 45.1, 43.0, 37.9, 32.5, 32.0;

HRMS calculated for $C_{23}H_{31}N_2O_3S$ $(M+H)^+$ 415.2055, found 415.2100.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(4-phenylpiperazin-1-yl)isothiazolidine 1,1-dioxide (3.24)



Procedure A; Yield 35%;

$[\alpha]_D^{25}$ = –95.33 (*c* = 0.60, CH_2Cl_2);

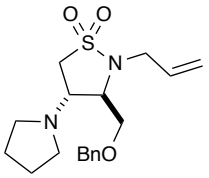
IR (neat): 3261, 2825, 1598, 1496, 1332, 1234, 1137, 1012, 696 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.36 (m, 2H), 7.36 – 7.31 (m, 3H), 7.31 – 7.24 (m, 3H), 6.94 – 6.87 (m, 3H), 4.65 (d, *J* = 8.6 Hz, 1H), 4.57 (dd, *J* = 19.0, 11.8 Hz, 2H), 3.79 – 3.69 (m, 3H), 3.55 (tdd, *J* = 9.5, 7.7, 3.9 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.24 – 3.07 (m, 5H), 2.77 – 2.57 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 151.0, 137.2, 129.2, 128.6, 128.2, 128.0, 120.2, 116.3, 73.5, 67.6, 64.7, 56.5, 49.6, 49.4, 45.3;

HRMS calculated for $C_{21}H_{27}N_3O_3SNa$ $(M+Na)^+$ 424.1671, found 424.1674.

(3*S*,4*R*)-2-Allyl-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.25)



Procedure B; Yield 29%;

$[\alpha]_D^{25} = -110.59$ ($c = 0.85$, CH_2Cl_2);

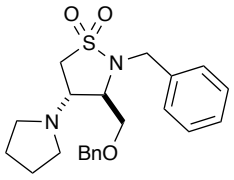
IR (neat): 2961, 2916, 2858, 1456, 1307, 1136, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 – 7.29 (m, 5H), 5.88 (dddd, *J* = 17.6, 10.1, 7.6, 5.2 Hz, 1H), 5.22 (ddd, *J* = 13.6, 11.4, 1.2 Hz, 2H), 4.55 (s, 2H), 3.94 (ddt, *J* = 15.5, 5.2, 1.4 Hz, 1H), 3.77 (dd, *J* = 15.5, 7.7 Hz, 1H), 3.69 – 3.62 (m, 2H), 3.61 – 3.51 (m, 2H), 3.29 (dd, *J* = 12.6, 7.4 Hz, 1H), 3.13 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.60 (m, 2H), 2.54 (m, 2H), 1.81 – 1.75 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.7, 133.0, 128.4, 127.8, 127.7, 119.2, 73.3, 70.2, 60.3, 57.7, 50.0, 47.1, 46.5, 23.4;

HRMS calculated for $C_{18}H_{26}N_2O_3SNa$ $(M+Na)^+$ 373.1562, found 373.1556.

(3*R*,4*S*)-2-Benzyl-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.26)



Procedure B; Yield 35%;

$[\alpha]_D^{25} = -35.20$ ($c = 2.00$, CH_2Cl_2);

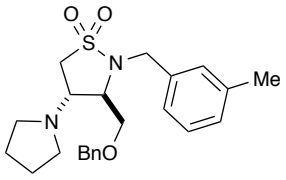
IR (neat): 2961, 2871, 1456, 1306, 1136, 1027, 736, 698 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 – 7.25 (m, 10H), 4.47 (d, J = 15.2 Hz, 1H), 4.39 (s, 2H), 4.34 (d, J = 15.3 Hz, 1H), 3.64 – 3.53 (m, 3H), 3.45 (dt, J = 9.2, 4.6 Hz, 1H), 3.34 (dd, J = 12.6, 7.7 Hz, 1H), 3.17 (dd, J = 12.6, 7.3 Hz, 1H), 2.55 – 2.47 (m, 2H), 2.46 – 2.38 (m, 2H), 1.76 – 1.68 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.7, 136.2, 128.6, 128.5, 128.4, 127.8, 127.7, 127.6, 73.2, 70.3, 60.1, 57.5, 49.8, 46.9, 23.4(2);

HRMS calculated for $C_{22}H_{28}N_2O_3SNa$ $(M+Na)^+$ 423.1718, found 423.1698.

(3*S*,4*R*)-3-((Benzyloxy)methyl)-2-(3-methylbenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.27)



Procedure B; Yield 37%;

$[\alpha]_D^{25} = -75.00$ ($c = 0.88$, CH_2Cl_2);

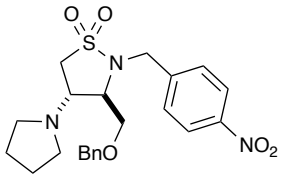
IR (neat): 2920, 2864, 1452, 1303, 1134, 748 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 1H), 4.44 (d, *J* = 15.1 Hz, 1H), 4.39 (d, *J* = 1.2 Hz, 2H), 4.29 (d, *J* = 15.2 Hz, 1H), 3.65 – 3.53 (m, 3H), 3.45 (td, *J* = 5.5, 3.7 Hz, 1H), 3.34 (dd, *J* = 12.6, 7.7 Hz, 1H), 3.18 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.53 – 2.51 (m, 2H), 2.47 – 2.41 (m, 2H), 2.29 (s, 3H), 1.73 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.1, 137.8, 136.0, 129.3, 128.4, 128.4, 128.3, 127.7, 127.6, 125.6, 73.2, 70.2, 60.0, 57.5, 49.8, 46.9, 46.7, 23.4, 21.3;

HRMS calculated for $C_{23}H_{30}N_2O_3SNa$ $(M+Na)^+$ 437.1875, found 437.1875.

(3*S*,4*R*)-3-((Benzyloxy)methyl)-2-(4-nitrobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.28)



Procedure B; Yield 87%;

$[\alpha]_D^{25}$ = –46.03 (*c* = 2.44, CH_2Cl_2);

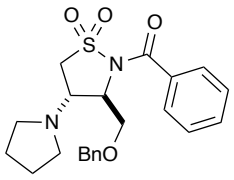
IR (neat): 2960, 2910, 2806, 1601, 1517, 1346, 1346, 1306, 1136, 860, 734 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 – 8.07 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.21 – 7.16 (m, 2H), 4.57 (d, *J* = 16.1 Hz, 1H), 4.43 (d, *J* = 16.1 Hz, 1H), 4.34 (s, 2H), 3.61 (m, 2H), 3.55 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.46 (td, *J* = 5.8, 3.9 Hz, 1H), 3.36 (dd, *J* = 12.5, 7.6 Hz, 1H), 3.20 (dd, *J* = 12.5, 7.8 Hz, 1H), 2.61 – 2.44 (m, 4H), 1.77 (dd, *J* = 6.1, 3.2 Hz, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.3, 144.5, 137.2, 128.9, 128.4, 128.0, 127.7, 123.6, 73.4, 71.1, 61.6, 57.5, 50.0, 46.9, 46.5, 23.4;

HRMS calculated for $C_{22}H_{27}N_3O_5SNa$ $(M+Na)^+$ 468.1569, found 468.1566.

((3*R*,4*S*)-3-((Benzyloxy)methyl)-1,1-dioxido-4-(pyrrolidin-1-yl)isothiazolidin-2-yl)(phenyl)methanone (3.29)



Procedure C; Yield 56%;

$[\alpha]_D^{25}$ = +15.88 (*c* = 2.02, CH_2Cl_2);

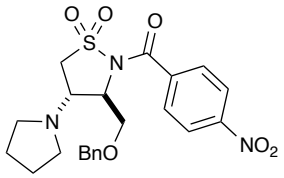
IR (neat): 2962, 2872, 1678, 1450, 1339, 1290, 1124, 1026, 734, 696 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 – 7.80 (m, 2H), 7.57 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.38 – 7.28 (m, 5H), 4.87 (dt, *J* = 6.4, 3.9 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 3.90 (dt, *J* = 8.8, 6.5 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.57 (dd, *J* = 12.6, 6.6 Hz, 1H), 3.37 (dd, *J* = 12.6, 8.7 Hz, 1H), 2.73 – 2.60 (m, 4H), 1.81 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.8, 137.8, 134.7, 132.6, 128.6, 128.4, 128.3, 127.7, 127.5, 73.3, 68.2, 59.6, 55.7, 50.0, 49.8, 23.5;

HRMS calculated for $C_{22}H_{27}N_2O_4S$ $(M+H)^+$ 415.1692, found 415.1691.

(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-nitrophenyl)methanone (3.30)



Procedure C; Yield 96%;

$[\alpha]_D^{25}$ = +8.82 (*c* = 1.23, CH_2Cl_2);

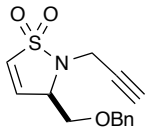
IR (neat): 2961, 2871, 1678, 1521, 1344, 1308, 1128, 736 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.35 – 8.28 (m, 2H), 7.95 – 7.89 (m, 2H), 7.37 – 7.31 (m, 5H), 4.85 (dt, *J* = 5.7, 3.7 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 3.90 – 3.78 (m, 3H), 3.64 (dd, *J* = 12.8, 6.5 Hz, 1H), 3.41 (dd, *J* = 12.8, 8.0 Hz, 1H), 2.73 – 2.59 (m, 4H), 1.86 – 1.83 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.9, 149.9, 140.1, 137.6, 129.5, 128.5, 127.9, 127.6, 123.5, 73.4, 68.0, 59.8, 56.3, 50.2, 30.94, 23.5;

HRMS calculated for $C_{22}H_{25}N_3O_6SNa$ $(M+Na)^+$ 482.1362, found 482.1364.

(*R*)-3-((Benzyloxy)methyl)-2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (3.31)



Procedure B; Yield 84%;

$[\alpha]_D^{25}$ = +69.33 (*c* = 2.25, CH_2Cl_2);

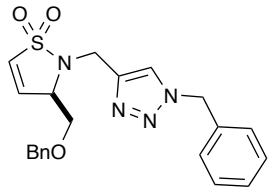
IR (neat): 3271, 2864, 1296, 1157, 1107 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.36 (m, 2H), 7.35 – 7.30 (m, 3H), 6.89 (dd, *J* = 6.9, 2.2 Hz, 1H), 6.74 (dd, *J* = 6.9, 2.0 Hz, 1H), 4.58 (d, *J* = 1.8 Hz, 2H), 4.48 (tt, *J* = 6.2, 2.2 Hz, 1H), 4.17 (dd, *J* = 18.0, 2.4 Hz, 1H), 4.04 (dd, *J* = 18.0, 2.2 Hz, 1H), 3.76 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.60 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.33 (t, *J* = 2.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 137.2, 128.6, 128.1, 127.7, 127.5, 77.1, 73.9, 73.7, 70.7, 61.8, 33.9;

HRMS calculated for $C_{14}H_{15}NO_3SNa$ $(M+Na)^+$ 300.0670, found 300.0668.

(*R*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.32)



Into an r. b. flask was added sulfonamide **3.31** (200 mg, 0.72 mmol) and benzyl azide (191 mg, 1.440 mmol) in CH_2Cl_2/^{t}BuOH (1.25 mL/1.25 mL). The aq. solution mixture of $CuSO_4$•$5H_2O$ (36 mg, 0.14 mmol) and (+)-sodim *L*-ascorbate (43 mg, 0.217 mmol) in water (1.25 mL) was added into the previous flask. The resulting mixture was stirred at rt for 12 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexane:EtOAc) afforded the desired product **3.32**.

Yield 97%;

$[\alpha]_D^{25}$ = +61.68 (*c* = 2.80, CH_2Cl_2);

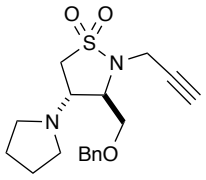
IR (neat): 3086, 2860, 1454, 1290, 1153, 1105, 741 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.64 (s, 1H), 7.38 – 7.33 (m, 5H), 7.31 (t, *J* = 6.0 Hz, 3H), 7.24 (dd, *J* = 7.1, 2.4 Hz, 2H), 6.85 (dd, *J* = 6.9, 2.2 Hz, 1H), 6.66 (dd, *J* = 6.9, 2.0 Hz, 1H), 5.52 (d, *J* = 14.8 Hz, 1H), 5.43 (d, *J* = 14.8 Hz, 1H), 4.62 – 4.51 (m, 2H), 4.52 – 4.47 (m, 2H), 4.30 (ddd, *J* = 8.9, 4.9, 2.1 Hz, 1H), 3.73 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.52 (dd, *J* = 9.7, 6.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.0, 138.0, 137.3, 134.4, 129.1, 128.8, 128.5, 128.0, 127.9, 127.7, 127.0, 124.0, 73.5, 69.6, 61.6, 54.3, 38.3;

HRMS calculated for $C_{21}H_{22}N_4O_3SNa$ $(M+Na)^+$ 433.1310, found 433.1308.

(3*R*,4*S*)-3-((Benzyloxy)methyl)-2-(prop-2-yn-1-yl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.33)



Procedure A; Yield 48%;

$[\alpha]_D^{25} = -34.80$ (c = 1.25, CH_2Cl_2);

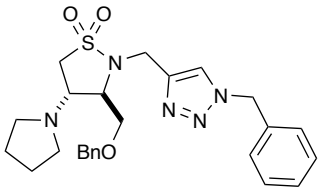
IR (neat): 3333, 2920, 2872, 1132, 1137, 912, 741 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.34 (m, 3H), 7.34 – 7.29 (m, 2H), 4.58 (s, 2H), 4.23 (dd, J = 18.1, 2.4 Hz, 1H), 3.93 (dd, J = 18.1, 2.4 Hz, 1H), 3.81 (dd, J = 9.7, 2.6 Hz, 1H), 3.76 (td, J = 7.1, 2.5 Hz, 1H), 3.69 (dd, J = 9.7, 6.8 Hz, 1H), 3.62 (dt, J = 8.8, 7.3 Hz, 1H), 3.27 (dd, J = 12.2, 7.2 Hz, 1H), 3.11 (dd, J = 12.2, 8.9 Hz, 1H), 2.66 – 2.56 (m, 4H), 2.32 (t, J = 2.4 Hz, 1H), 1.81 – 1.75 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.8, 128.5, 127.8, 127.6, 77.9, 73.5, 73.4, 71.3, 60.5, 57.2, 49.8, 45.8, 35.5, 23.5;

HRMS calculated for $C_{18}H_{24}N_2O_3SNa$ $(M+Na)^+$ 371.1405, found 371.1402.

(3*R*,4*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.34)



Into an r. b. flask was added sulfonamide **3.33** (137 mg, 0.39 mmol) and benzyl azide (104 mg, 0.780 mmol) in CH_2Cl_2/^{t}BuOH (0.7 mL/0.7 mL). The aq. solution mixture of $CuSO_4$•$5H_2O$ (20 mg, 0.08 mmol) and (+)-sodim *L*-ascorbate (23 mg, 0.12 mmol) in water (0.7 mL) was added into the previous flask. The resulting mixture was stirred at rt for 12 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexane:EtOAc) afforded the desired product **3.34**.

Yield 84%;

$[\alpha]_D^{25} = -17.95$ ($c = 2.98$, CH_2Cl_2);

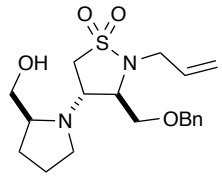
IR (neat): 2951, 2934, 1454, 1359, 1303, 1135, 1047, 750 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (s, 1H), 7.37 – 7.32 (m, 5H), 7.32 – 7.29 (m, 3H), 7.24 – 7.20 (m, 2H), 5.47 (d, J = 14.8 Hz, 1H), 5.41 (d, J = 14.8 Hz, 1H), 4.58 (d, J = 16.2 Hz, 1H), 4.48 (d, J = 15.9 Hz, 1H), 4.46 (d, J = 1.1 Hz, 2H), 3.74 (dd, J = 10.3, 3.2 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.63 (dd, J = 10.4, 4.9 Hz, 1H), 3.53 (m, 1H), 3.26 (dd, J = 12.5, 7.7 Hz, 1H), 3.02 (dd, J = 12.5, 7.2 Hz, 1H), 2.43 (m, 4H), 1.68 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.7, 137.9, 134.6, 129.1, 128.7, 128.4, 127.9, 127.7, 127.5, 123.7, 73.1, 69.2, 60.4, 57.2, 54.1, 49.8, 46.6, 38.9, 23.4;

HRMS calculated for $C_{25}H_{31}N_5O_3SNa$ $(M+Na)^+$ 504.2045, found 504.2046.

(3*R*,4*S*)-2-Allyl-3-((benzyloxy)methyl)-4-((*S*)-2-(hydroxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.35)



Procedure B; Yield 26%;

$[\alpha]_D^{25} = -58.00$ (*c* = 1.50, CH_2Cl_2);

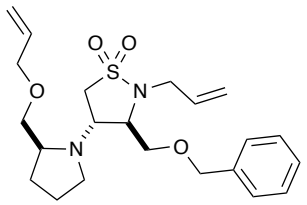
IR (neat): 3475, 2984, 2867, 1497, 1304, 1134, 912, 742 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.30 (m, 5H), 5.92 – 5.82 (m, 1H), 5.23 (dd, *J* = 6.3, 1.4 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 2H), 3.97 (q, *J* = 7.9 Hz, 1H), 3.88 (ddt, *J* = 15.7, 5.1, 1.4 Hz, 1H), 3.69 (dd, *J* = 15.5, 7.8 Hz, 1H), 3.67 (dd, *J* = 10.8, 4.7 Hz, 1H), 3.62 – 3.59 (m, 1H), 3.60 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.46 (dt, *J* = 7.7, 4.4 Hz, 1H), 3.37 (d, *J* = 10.9 Hz, 1H), 3.23 (dd, *J* = 12.5, 8.2 Hz, 1H), 3.14 (dd, *J* = 12.5, 7.9 Hz, 1H), 2.97 – 2.90 (m, 1H), 2.81 (m, 1H), 2.64 (dd, *J* = 16.3, 7.4 Hz, 1H), 2.41 (d, *J* = 15.3 Hz, 1H), 1.84 (tt, *J* = 9.7, 5.9 Hz, 1H), 1.80 – 1.71 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 132.8, 128.5, 128.1, 128.0, 119.4, 73.5, 68.9, 62.6, 62.4, 60.0, 55.3, 46.6, 46.2, 44.0, 27.8, 24.1;

HRMS calculated for $C_{19}H_{28}N_2O_4SNa$ $(M+Na)^+$ 403.1668, found 403.1667.

(3*R*,4*S*)-2-Allyl-4-((*S*)-2-((allyloxy)methyl)pyrrolidin-1-yl)-3-((benzyloxy)methyl)isothiazolidine 1,1-dioxide (3.36)



Procedure B; Yield 73%;

$[\alpha]_D^{25} = -80.85$ (c = 1.29, CH_2Cl_2);

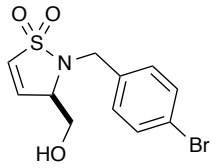
IR (neat): 2961, 2871, 1678, 1521, 1344, 1308, 1128, 736 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.29 (m, 5H), 5.96 – 5.81 (m, 2H), 5.21 (m, 4H), 4.58 – 4.49 (m, 2H), 4.10 (dd, J = 16.1, 8.0 Hz, 1H), 3.98 – 3.94 (m, 3H), 3.76 (dd, J = 15.7, 8.5 Hz, 1H), 3.73 (dd, J = 10.2, 2.6 Hz, 1H), 3.64 (dd, J = 10.2, 5.6 Hz, 1H), 3.47 (ddd, J = 8.1, 5.6, 2.6 Hz, 1H), 3.33 – 3.29 (m, 2H), 3.24 (dd, J = 12.6, 8.4 Hz, 1H), 3.13 (dd, J = 12.6, 7.6 Hz, 1H), 2.92 – 2.86 (m, 1H), 2.82 (ddd, J = 11.7, 8.0, 5.8 Hz, 1H), 2.58 (dd, J = 16.3, 8.2 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.74 (tdd, J = 20.8, 10.6, 6.3 Hz, 2H), 1.60 – 1.51 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.8, 134.6, 133.2, 128.4, 127.8, 127.7, 119.0, 117.1, 74.2, 73.3, 72.2, 69.8, 60.9, 60.4, 55.3, 46.4, 46.0, 44.0, 28.5, 23.4;

HRMS calculated for $C_{22}H_{32}N_2O_4SNa$ $(M+Na)^+$ 443.1980, found 443.1877.

(*R*)-2-(4-bromobenzyl)-3-(hydroxymethyl)-2,3-dihydroisothiazole 1,1-dioxide (3.37)



Into an r. b. flask was added sulfonamide **3.7** (130 mg, 0.318 mmol) in CH_2Cl_2 (3.2 mL). BCl_3 solution (6.4 mL, 0.64 mmol) was added slowly at -78 ºC in dry ice/acetone bath and the temperature was let to rise slowly to rt. The reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexane:EtOAc) afforded the desired product **3.37**.

Yield 76%;

$[\alpha]_D^{25}$ = +49.40 (*c* = 1.00, CH_2Cl_2);

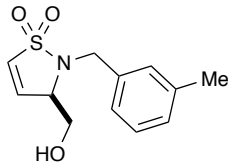
IR (neat): 3500, 2871, 1678, 1521, 1348, 1283, 1149, 1070 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.51 (d, *J* = 6.6 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.83 (dd, *J* = 7.0, 2.0 Hz, 1H), 6.80 (dd, *J* = 7.0, 1.7 Hz, 1H), 4.52 (d, *J* = 15.5 Hz, 1H), 4.30 (d, *J* = 15.5 Hz, 1H), 4.09 – 4.06 (m, 1H), 3.69 – 3.54 (m, 2H), 1.71 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.2, 134.7, 132.1, 130.2, 128.0, 122.4, 64.5, 61.9, 46.8;

HRMS calculated for $C_{11}H_{12}BrNO_3SNa$ $(M+Na)^+$ 339.9619, found 339.9625.

(*R*)-3-(hydroxymethyl)-2-(3-methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.38)



Into an r. b. flask was added sulfonamide **3.9** (25 mg, 0.073 mmol) in CH_2Cl_2 (2 mL). BCl_3 solution (1.5 mL, 0.15 mmol) was added slowly at -78 ºC in dry ice/acetone bath and the temperature was let to rise slowly to rt. The reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:2 hexane:EtOAc) afforded the desired product **3.38**.

Yield 56%;

$[\alpha]_D^{25}$ = +18.00 (*c* = 0.50, CH_2Cl_2);

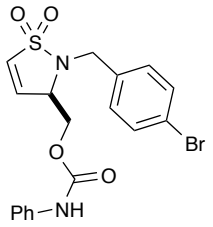
IR (neat): 3500, 2920, 2867, 1279, 1151, 1130, 783 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.30 – 7.25 (m, 1H), 7.25 – 7.21 (m, 2H), 7.17 – 7.15 (d, *J* = 7.3 Hz, 1H), 6.83 – 6.79 (m, 2H), 4.55 (d, *J* = 15.2 Hz, 1H), 4.25 (d, *J* = 15.2 Hz, 1H), 4.09 – 4.07 (m, 1H), 3.63 – 3.48 (m, 2H), 2.37 (s, 3H), 1.68 (s, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.9, 137.5, 135.5, 129.1, 129.0, 128.9, 128.0, 125.5, 64.6, 61.7, 47.4, 21.4;

HRMS calculated for $C_{12}H_{15}NO_3SNa$ $(M+Na)^+$ 276.0670, found 276.0675.

(*R*)-(2-(4-bromobenzyl)-1,1-dioxido-2,3-dihydroisothiazol-3-yl)methyl phenylcarbamate (3.39)



Into an r. b. flask was added sulfonamide **3.37** (10 mg, 0.031 mmol) in CH_2Cl_2 (1 mL). Phenyl isocyanate (3.8 μL, 0.035 mmol) and Et_3N (1 μL, 0.007 mmol) were added and refluxed for 12 h. The solvent removed under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) afforded the desired product **3.39**.

Yield 63%;

$[\alpha]_D^{25}$ = +172.00 (*c* = 0.50, CH_2Cl_2);

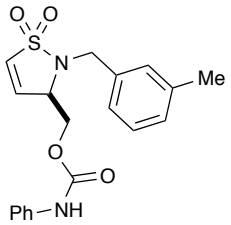
IR (neat): 3335, 2918, 2871, 1732, 1537, 1500, 1445, 1313, 1217, 1153 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.49 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.30 (m, 6H), 7.11 (tt, *J* = 5.2, 3.0 Hz, 1H), 6.83 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.64 (s, 1H), 4.44 (d, *J* = 1.9 Hz, 2H), 4.30 – 4.25 (m, 1H), 4.22 – 4.16 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 152.5, 137.1, 135.9, 134.3, 132.0, 130.2, 129.1, 128.3, 124.1, 122.3, 118.8, 61.5, 46.0;

HRMS calculated for $C_{18}H_{17}BrN_2O_4SNa$ $(M+Na)^+$ 458.9990, found 458.9983.

(*R*)-(2-(3-methylbenzyl)-1,1-dioxido-2,3-dihydroisothiazol-3-yl)methyl phenylcarbamate (3.40)



Into an r. b. flask was added sulfonamide **3.38** (10 mg, 0.031 mmol) in CH_2Cl_2 (1 mL). Phenyl isocyanate (30 μL, 0.276 mmol) and Et_3N (6 μL, 0.043 mmol) were added and the reaction mixture was refluxed for 12 h. The solvent removed under reduced pressure and purified by flash chromatography (3:1 hexane:EtOAc) afforded the desired product **3.40**.

Yield 98%;

$[\alpha]_D^{25}$ = +101.93 (*c* = 1.50, CH_2Cl_2);

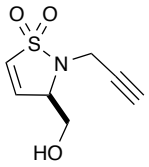
IR (neat): 3335, 2915, 1732, 1601, 1537, 1445, 1289, 1217, 1155, 756 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 – 7.30 (m, 4H), 7.27 – 7.21 (m, 3H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.10 (tt, *J* = 6.7, 1.7 Hz, 1H), 6.82 – 6.79 (m, 2H), 6.70 (s, 1H), 4.49 (d, *J* = 15.3 Hz, 1H), 4.41 (d, *J* = 15.3 Hz, 1H), 4.27 – 4.22 (m, 1H), 4.20 – 4.14 (m, 2H), 2.34 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 152.6, 138.7, 137.2, 136.1, 135.0, 129.2, 129.1, 129.0, 128.8, 128.3, 125.5, 123.9, 118.8, 62.0, 61.3, 46.3, 21.4;

HRMS calculated for $C_{19}H_{20}N_2O_4SNa$ $(M+Na)^+$ 395.1042, found 395.0900.

(*R*)-3-(Hydroxymethyl)-2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (3.41)



Into an r. b. flask was added sulfonamide **3.31** (239 mg, 0.862 mmol) in CH_2Cl_2 (15 mL). BCl_3 solution (1.7 mL, 1.7 mmol) was added slowly at -78 ºC in dry ice/acetone bath and the temperature was let to rise slowly to rt. The reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:10 hexane:EtOAc) afforded the desired product **3.41**.

Yield 59%; Mp 110 ºC;

$[\alpha]_D^{25}$ = +13.42 (*c* = 2.43, CH_2Cl_2);

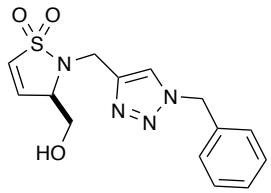
IR (neat): 3320, 3271, 3087, 2926, 2876, 1286, 1155, 1121, 742 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.87 (dd, *J* = 6.9, 2.3 Hz, 1H), 6.78 (dd, *J* = 6.9, 2.0 Hz, 1H), 4.39 (tt, *J* = 4.1, 2.2 Hz, 1H), 4.10 (d, *J* = 2.5 Hz, 2H), 3.97 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.85 (ddd, *J* = 11.9, 8.3, 4.0 Hz, 1H), 2.38 (t, *J* = 2.7 Hz, 1H), 2.06 (dd, *J* = 8.5, 4.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.6, 128.0, 76.9, 74.1, 64.5, 62.2, 33.9;

HRMS calculated for $C_7H_9NO_3SNa$ $(M+Na)^+$ 210.0201, found 210.0196.

(*R*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(hydroxymethyl)-2,3-dihydroisothiazole 1,1-dioxide (3.42)



Into an r. b. flask was added sulfonamide **3.41** (134 mg, 0.720 mmol) and benzyl azide (191 mg, 1.440 mmol) in CH_2Cl_2/^{t}BuOH (1.3 mL/1.3 mL). The aq. solution mixture of $CuSO_4$•$5H_2O$ (36 mg, 0.140 mmol) and (+)-sodim *L*-ascorbate (43 mg, 0.220 mmol) in water (1.3 mL) was added into the previous flask. The resulting mixture was stirred at rt for 12 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:2 hexane:EtOAc) afforded the desired product **3.42**.

Yield 61%; Mp 174 ºC; $[\alpha]_D^{25}$ = +0.99 (*c* = 2.42, CH_2Cl_2);

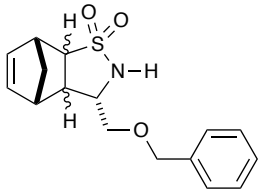
IR (neat): 3320, 3087, 2926, 2876, 1608, 1456, 1285, 1151, 742 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (s, 1H), 7.42 – 7.35 (m, 3H), 7.29 – 7.25 (m, 2H), 6.78 (dd, *J* = 7.0, 2.1 Hz, 1H), 6.68 (dd, *J* = 7.0, 2.1 Hz, 1H), 5.52 (s, 2H), 4.72 (d, *J* = 16.3 Hz, 1H), 4.44 (d, *J* = 16.3 Hz, 1H), 4.30 (td, *J* = 5.5, 2.1 Hz, 1H), 3.93 (dd, *J* = 12.2, 3.5 Hz, 1H), 3.80 (dd, *J* = 12.2, 5.0 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.6, 137.4, 134.1, 129.2, 128.9, 128.1, 127.6, 123.2, 65.8, 62.7, 54.4, 37.6;

HRMS calculated for $C_{14}H_{16}N_4O_3SNa$ $(M+Na)^+$ 343.0841, found 343.0842.

(3*S*,3a*S*,4*S*,7*R*,7a*S*)-3-((Benzyloxy)methyl)-2,3,3a,4,7,7a-hexahydro-4,7-methanobenzo[*d*]isothiazole 1,1-dioxide (3.43)



Into an r. b. flask was added sulfonamide **(*S*)-3.3** (22 mg, 0.093 mmol) in anhydrous toluene (1 mL). Cyclopentadiene (60 μL, 0.735 mmol) and Et_2AlCl (0.1 mL, 0.180 mmol) were added and the resulting mixture was stirred at 55 ºC for 24 h. The reaction was quenched with water and sat. aq. $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (2:1 hexane:EtOAc) afforded the desired product **3.43**.

Yield 36%;

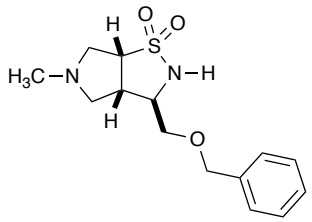
IR (neat): 3273, 2974, 2868, 1452, 1302, 1146, 1092, 751 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.41 – 7.29 (m, 5H), 6.48 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.30 (dd, *J* = 5.8, 3.1 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.21 (d, *J* = 6.9 Hz, 1H), 3.83 (dd, *J* = 8.6, 4.0 Hz, 1H), 3.61 (dd, *J* = 9.5, 7.2 Hz, 1H), 3.57 (dd, *J* = 9.5, 7.4 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.24 – 3.15 (m, 2H), 3.13 (m, 1H), 1.65 (dt, *J* = 8.9, 1.8 Hz, 1H), 1.44 (dt, *J* = 8.8, 1.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.7, 136.4, 134.2, 128.5, 127.9, 127.8, 73.5, 71.8, 64.2, 56.3, 51.3, 49.1, 47.0, 46.2;

HRMS calculated for $C_{16}H_{20}NO_3S$ $(M+H)^+$ 306.1164, found 306.1159.

(3*R*,3a*S*,6a*R*)-3-((Benzyloxy)methyl)-5-methylhexahydro-2*H*-pyrrolo[3,4-*d*]isothiazole 1,1-dioxide (3.44)



Into an r. b. flask was added sulfonamide **(*R*)-3.3** (100 mg, 0.418 mmol) in anhydrous DMSO (0.8 mL). Sarcosine (190 mg, 2.133 mmol), paraformaldehyde (150 mg, 4.995 mmol) and anhydrous $MgSO_4$ (200 mg, 1.662 mmol) were added and the reaction mixture was kept in microwave at 150 ºC for 1 h. The reaction was quenched with water and sat. aq. brine and diethyl ether. The organic layer was washed with water (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:3 acetone:EtOAc) afforded the desired product **3.44**.

Yield 10%;

$[\alpha]_D^{25}$ = +0.32 (*c* = 0.10, CH_2Cl_2);

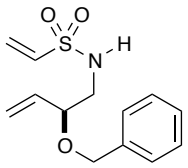
IR (neat): 3232, 2945, 2791, 1452, 1307, 1141, 1093, 746 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 3H), 4.67 (d, *J* = 8.4 Hz, 1H), 4.57 (s, 2H), 3.72 – 3.67 (m, 1H), 3.66 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.60 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.47 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.45 – 3.40 (m, 1H), 3.16 (dtd, *J* = 9.7, 6.1, 1.6 Hz, 1H), 2.77 (d, *J* = 9.5 Hz, 1H), 2.41 (dd, *J* = 10.8, 8.0 Hz, 1H), 2.34 (s, 3H), 2.33 (dd, *J* = 9.5, 6.1 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.3, 128.6, 128.1, 127.8, 73.5, 69.5, 61.9, 61.1, 58.8, 57.0, 47.2, 41.2;

HRMS calculated for $C_{14}H_{20}N_2O_3SNa$ $(M+Na)^+$ 319.1092, found 319.1092.

(*S*)-*N*-(2-(Benzyloxy)but-3-en-1-yl)ethenesulfonamide (3.49)



Yield 49%;

$[\alpha]_D^{25}$ = +0.25 (*c* = 0.50, CH_2Cl_2);

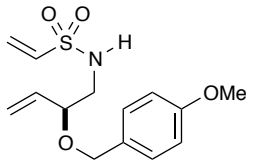
IR (neat): 3320, 2935, 2840, 1520, 1336, 1263, 1152 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.35 (m, 2H), 7.32 (td, *J* = 6.1, 1.3 Hz, 3H), 6.42 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.22 (d, *J* = 16.6 Hz, 1H), 5.89 (d, *J* = 9.8 Hz, 1H), 5.74 (ddd, *J* = 17.1, 10.5, 7.4 Hz, 1H), 5.42 – 5.39 (m, 1H), 5.38 (t, *J* = 0.6 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.02 – 3.95 (m, 1H), 3.20 (ddd, *J* = 13.1, 8.1, 3.8 Hz, 1H), 3.06 (ddd, *J* = 13.0, 8.2, 4.1 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.6, 135.8, 134.9, 128.6, 128.1, 128.0, 126.6, 120.1, 78.6, 70.5, 46.9;

HRMS calculated for $C_{13}H_{18}NO_3S$ $(M+H)^+$ 268.1007, found 268.1010.

(*S*)-*N*-(2-((4-Methoxybenzyl)oxy)but-3-en-1-yl)ethenesulfonamide (3.50)



Yield 50%;

$[\alpha]_D^{25}$ = +28.00 (*c* = 0.50, CH_2Cl_2);

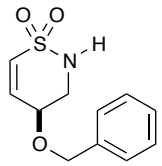
IR (neat): 3315, 2939, 2845, 1513, 1331, 1248, 1148, 739 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.24 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.42 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.22 (d, *J* = 16.6 Hz, 1H), 5.89 (d, *J* = 9.9 Hz, 1H), 5.73 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H), 5.40 (dt, *J* = 6.9, 1.2 Hz, 1H), 5.37 (s, 1H), 4.63 (dd, *J* = 7.8, 4.0 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.29 (d, *J* = 11.1 Hz, 1H), 3.97 (dt, *J* = 8.2, 3.8 Hz, 1H), 3.82 (s, 3H), 3.18 (ddd, *J* = 12.9, 8.1, 3.8 Hz, 1H), 3.03 (ddd, *J* = 12.8, 8.2, 4.1 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.4, 135.8, 135.0, 129.7, 129.6, 126.6, 119.96, 113.9, 78.3, 70.2, 55.3, 46.9;

HRMS calculated for $C_{14}H_{20}NO_4SNa$ $(M+Na)^+$ 298.1113, found 298.1116.

(*S*)-4-(Benzyloxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.51)



Yield 63%;

$[\alpha]_D^{25}$ = +65.77 (*c* = 5.88, CH_2Cl_2);

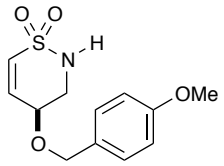
IR (neat): 3254, 2926, 1558, 1506, 1317, 1174, 1145, 912 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.43 – 7.31 (m, 5H), 6.70 (dd, *J* = 11.0, 1.1 Hz, 1H), 6.45 (ddd, *J* = 11.0, 4.5, 1.8 Hz, 1H), 4.71 – 4.64 (m, 1H), 4.63 (d, *J* = 1.0 Hz, 2H), 3.86 – 3.81 (m, 1H), 3.79 (dtd, *J* = 4.4, 3.0, 1.3 Hz, 1H), 3.71 – 3.64 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 136.8, 135.0, 131.4, 128.8, 128.5, 127.8, 71.7, 65.1, 46.3;

HRMS calculated for $C_{11}H_{13}NO_3SNa$ $(M+Na)^+$ 262.0514, found 262.0520.

(*S*)-4-((4-Methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.52)



Yield 73%;

$[\alpha]_D^{25}$ = +30.50 (*c* = 2.50, CH_2Cl_2);

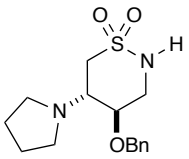
IR (neat): 3250, 2929, 1555, 1285, 1151, 742 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.30 – 7.25 (m, 2H), 6.96 – 6.90 (m, 2H), 6.70 (dd, *J* = 11.0, 1.1 Hz, 1H), 6.43 (ddd, *J* = 11.0, 4.5, 1.8 Hz, 1H), 4.70 – 4.63 (m, 1H), 4.57 (d, *J* = 1.2 Hz, 2H), 3.84 (s, 3H), 3.83 – 3.76 (m, 2H), 3.69 – 3.63 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.7, 135.2, 131.2, 129.5, 128.8, 114.1, 71.4, 64.8, 55.3, 46.4;

HRMS calculated for $C_{12}H_{15}NO_4SNa$ $(M+Na)^+$ 292.0619, found 292.0625.

(4*R*,5*S*)-4-(Benzyloxy)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.53)



Procedure A; Yield 39%;

$[\alpha]_D^{25} = -76.91$ ($c = 0.75$, CH_2Cl_2);

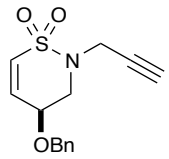
IR (neat): 3259, 2964, 2950, 2796, 1406, 1356, 1153, 1099, 742 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 – 7.30 (m, 5H), 4.64 (d, J = 2.5 Hz, 2H), 4.52 (d, J = 7.9 Hz, 1H), 3.89 (ddd, J = 14.6, 11.0, 1.7 Hz, 1H), 3.53 (td, J = 4.4, 1.6 Hz, 1H), 3.47 (dd, J = 14.3, 3.9 Hz, 1H), 3.31 (dd, J = 14.4, 4.6 Hz, 1H), 3.25 (dt, J = 15.6, 3.2 Hz, 1H), 3.04 (d, J = 3.2 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.60 – 2.50 (m, 2H), 1.85 – 1.74 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.4, 128.7, 128.2, 127.7, 71.8, 70.8, 63.0, 51.7, 48.4, 43.8, 23.5;

HRMS calculated for $C_{15}H_{22}N_2O_3SNa$ $(M+Na)^+$ 333.1249, found 333.1254.

(*S*)-4-(Benzyloxy)-2-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.54)



Procedure B; Yield 87%;

$[\alpha]_D^{25}$ = +93.33 (*c* = 1.50, CH_2Cl_2);

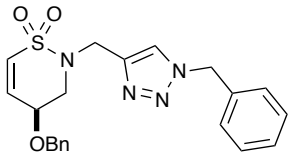
IR (neat): 3283, 2864, 1342, 1329, 1177, 1148, 912, 744 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.32 (m, 5H), 6.57 (dd, *J* = 10.9, 1.7 Hz, 1H), 6.43 (ddd, *J* = 10.9, 3.7, 1.4 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.27 (ddd, *J* = 16.7, 2.5, 0.6 Hz, 1H), 4.11 (ddd, *J* = 15.4, 4.0, 1.5 Hz, 1H), 4.05 (dd, *J* = 16.7, 2.5 Hz, 1H), 4.04 – 4.00 (m, 1H), 3.94 (dd, *J* = 15.4, 4.3 Hz, 1H), 2.39 (t, *J* = 2.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 136.9, 136.0, 128.8, 128.7, 128.6, 128.3, 127.8, 74.2, 72.0, 65.8, 47.5, 39.3;

HRMS calculated for $C_{14}H_{15}NO_3SNa$ $(M+Na)^+$ 300.0670, found 300.0670.

(*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-(benzyloxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.55)



Into an r. b. flask were added sulfonamide **3.51** (140 mg, 0.505 mmol) and benzyl azide (140 mg, 1.051 mmol) in CH_2Cl_2/^{t}BuOH (0.9 mL/0.9 mL). The aq. solution mixture of $CuSO_4$•$5H_2O$ (26 mg, 0.104 mmol) and (+)-sodim *L*-ascorbate (30 mg, 0.151 mmol) in water (0.9 mL) was added into the previous flask. The resulting mixture was stirred at rt for 12 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexane:EtOAc) afforded the desired product **3.55**.

Yield 99%;

$[\alpha]_D^{25}$ = +35.20 (*c* = 1.25, CH_2Cl_2);

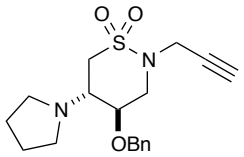
IR (neat): 3138, 3031, 2943, 2866, 1454, 1335, 1146, 1095, 1049, 912 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (s, 1H), 7.42 – 7.30 (m, 8H), 7.30 – 7.25 (m, 2H), 6.56 (dd, *J* = 10.9, 1.7 Hz, 1H), 6.36 (dd, *J* = 11.0, 3.6 Hz, 1H), 5.51 (d, *J* = 1.8 Hz, 2H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H), 4.58 (d, *J* = 15.0 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 3.98 (tdd, *J* = 4.9, 3.5, 1.8 Hz, 1H), 3.88 (ddd, *J* = 15.2, 4.9, 1.2 Hz, 1H), 3.78 (dd, *J* = 15.3, 4.5 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.7, 137.0, 136.4, 134.3, 129.2, 129.1, 128.9, 128.6, 128.2, 128.1, 127.9, 123.3, 71.9, 66.1, 54.3, 48.3, 44.0;

HRMS calculated for $C_{21}H_{22}N_4O_3SNa$ $(M+Na)^+$ 433.1310, found 433.1316.

(4*R*,5*S*)-4-(Benzyloxy)-2-(prop-2-yn-1-yl)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.56)



Procedure A; Yield 45%;

$[\alpha]_D^{25}$ = –20.86 (*c* = 1.75, CH_2Cl_2);

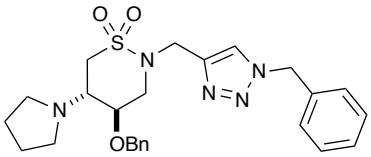
IR (neat): 3284, 2962, 2874, 1454, 1337, 1329, 1150, 1103, 899 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 – 7.35 (m, 4H), 7.34 – 7.29 (m, 1H), 4.70 (s, 2H), 4.16 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.92 – 3.87 (m, 1H), 3.87 (dd, *J* = 17.5, 2.4 Hz, 1H), 3.54 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.44 (dd, *J* = 13.9, 9.1 Hz, 1H), 3.37 (dd, *J* = 13.4, 3.9 Hz, 1H), 3.15 (dd, *J* = 13.3, 9.9 Hz, 1H), 2.71 – 2.60 (m, 4H), 2.36 (t, *J* = 2.5 Hz, 1H), 1.83 – 1.72 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.8, 128.5, 128.0, 127.9, 78.1, 74.3, 72.4, 72.2, 61.3, 48.9, 48.7, 47.0, 37.8, 23.6;

HRMS calculated for $C_{18}H_{24}N_2O_3SNa$ $(M+Na)^+$ 371.1405, found 371.1410.

(4*R*,5*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-(benzyloxy)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.57)



Into an r. b. flask were added sulfonamide **3.54** (31 mg, 0.112 mmol) and benzyl azide (31 mg, 0.233 mmol) in CH_2Cl_2/^{t}BuOH (0.2 mL/0.2 mL). The aq. solution mixture of $CuSO_4$•$5H_2O$ (4.2 mg, 0.017 mmol) and (+)-sodim *L*-ascorbate (5 mg, 0.0.25 mmol) in water (0.2 mL) was added into the previous flask. The resulting mixture was stirred at rt for 12 h. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (1:4 hexane:EtOAc) afforded the desired product **3.57**.

Yield 72%; $[\alpha]_D^{25}$ = –28.79 (*c* = 0.58, CH_2Cl_2);

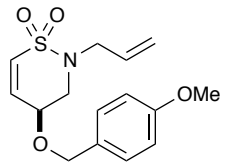
IR (neat): 2938, 2870, 1457, 1335, 1147, 1119, 1115, 1076, 917, 750 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.55 (s, 1H), 7.41 – 7.31 (m, 10H), 5.54 (d, *J* = 14.9 Hz, 1H), 5.48 (d, *J* = 14.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 3.1 Hz, 2H), 3.64 – 3.55 (m, 2H), 3.37 (m, 2H), 3.34 – 3.25 (m, 1H), 3.02 (dd, *J* = 14.3, 10.0 Hz, 1H), 2.66 – 2.53 (m, 4H), 1.79 – 1.71 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.8, 137.7, 134.3, 129.2, 128.9, 128.4, 128.1, 127.9, 127.8, 123.1, 72.6, 71.7, 61.6, 54.3, 49.3, 48.0, 47.5, 42.9, 23.6;

HRMS calculated for $C_{25}H_{31}N_5O_3SNa$ $(M+Na)^+$ 504.2045, found 504.2045.

(*S*)-2-Allyl-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.58)



Procedure B; Yield 84%;

$[\alpha]_D^{25}$ = +74.06 (*c* = 2.78, CH_2Cl_2);

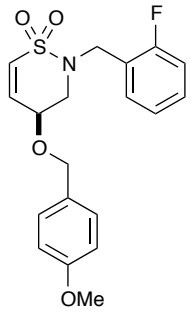
IR (neat): 3055, 2936, 2866, 1612, 1512, 1342, 1323, 1250, 1176, 1144, 1031, 820 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.27 – 7.22 (m, 2H), 6.93 – 6.88 (m, 2H), 6.58 (dd, *J* = 10.9, 1.8 Hz, 1H), 6.38 (ddt, *J* = 10.9, 3.5, 1.0 Hz, 1H), 5.90 – 5.77 (m, 1H), 5.30 (d, *J* = 1.4 Hz, 1H), 5.27 (dq, *J* = 8.4, 1.4 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.01 (ddt, *J* = 14.3, 5.4, 1.6 Hz, 1H), 3.90 (tdd, *J* = 4.4, 3.5, 1.8 Hz, 1H), 3.83 (s, 3H), 3.80 (dt, *J* = 7.0, 1.1 Hz, 1H), 3.79 3.75 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.6, 136.0, 132.7, 129.4, 129.3, 129.0, 119.9, 114.0, 71.5, 65.6, 55.3, 51.3, 47.4;

HRMS calculated for $C_{15}H_{19}NO_4SNa$ $(M+Na)^+$ 332.0932, found 332.0941.

(*S*)-2-(2-Fluorobenzyl)-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.59)



Procedure B; Yield 71%;

$[\alpha]_D^{25}$ = +87.13 (*c* = 2.09, CH_2Cl_2);

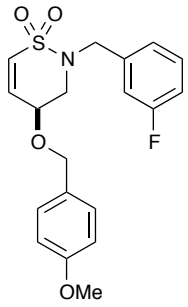
IR (neat): 3937, 2912, 1612, 1585, 1514, 1493, 1456, 1339, 1303, 1249, 1175, 1146, 1032, 760 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.45 (td, *J* = 7.6, 1.8 Hz, 1H), 7.32 (dddd, *J* = 8.2, 7.3, 5.3, 1.8 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.15 (td, *J* = 7.5, 1.2 Hz, 1H), 7.08 (ddd, *J* = 9.6, 8.2, 1.2 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.64 (dd, *J* = 10.9, 1.8 Hz, 1H), 6.43 – 6.38 (m, 1H), 4.59 (d, *J* = 14.7 Hz, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.91 (tdd, *J* = 4.5, 3.5, 1.8 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, *J* = 15.4, 4.5 Hz, 1H), 3.69 (ddd, *J* = 15.4, 4.6, 1.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.2 (d, $^1J_{C\text{-}F}$ = 245.9 Hz), 159.6, 136.2, 130.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.7 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.5, 129.4, 128.9, 124.4 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 122.9 (d, $^2J_{C\text{-}F}$ = 13.9 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 114.0, 71.6, 65.5, 55.3, 48.2, 45.9;

HRMS calculated for $C_{19}H_{20}FNO_4SNa$ $(M+Na)^+$ 400.0995, found 400.0999.

(*S*)-2-(3-Fluorobenzyl)-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.60)



Procedure B; Yield 98%;

$[\alpha]_D^{25}$ = +94.30 (*c* = 2.85, CH_2Cl_2);

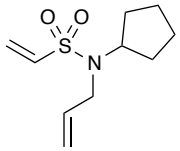
IR (neat): 2938, 1609, 1595, 1514, 1339, 1252, 1175, 1146, 1096, 1032, 768 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 (td, *J* = 7.9, 5.8 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.13 (ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.08 (dt, *J* = 9.4, 2.2 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.92 – 6.87 (m, 2H), 6.66 (dd, *J* = 10.9, 1.8 Hz, 1H), 6.45 (ddd, *J* = 11.0, 3.7, 1.6 Hz, 1H), 4.62 (d, *J* = 14.1 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 14.2 Hz, 1H), 3.84 (s, 4H), 3.76 (ddd, *J* = 15.5, 4.4, 1.0 Hz, 1H), 3.57 (ddd, *J* = 15.5, 3.5, 1.7 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.0 (d, $^1J_{C\text{-}F}$ = 245.1 Hz), 159.7, 138.1 (d, $^3J_{C\text{-}F}$ = 7.3 Hz), 135.9, 132.0 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 129.5, 129.2, 128.7, 124.3 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 114.0, 71.7, 65.5, 55.3, 51.9, 47.5;

HRMS calculated for $C_{19}H_{20}FNO_4SNa$ $(M+Na)^+$ 400.0995, found 400.0996.

_N_-Allyl-_N_-cyclopentylethenesulfonamide (3.61a)



Procedure D; Yield 86%;

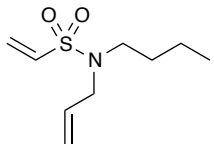
FTIR (neat): 3102, 3069, 1610, 1516, 1286, 1161 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.46 – 6.39 (m, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.90 – 5.84 (m, 2H), 5.29 – 5.23 (m, 1H), 5.16 (ddd, J = 10.2, 2.8, 1.4 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.71 (dt, J = 5.6, 1.5 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.70 – 1.61 (m, 2H), 1.60 – 1.49 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.7, 133.1, 125.8, 116.9, 59.1, 46.00, 29.7, 23.4;

HRMS calculated for $C_{10}H_{18}NO_2S$ $(M+H)^+$ 216.1058, found 216.1056.

***N*-Allyl-*N*-butylethenesulfonamide (3.61b)**



Procedure D; Yield 91%;

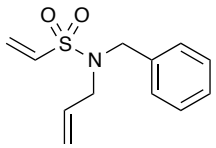
FTIR (neat): 3106, 3067, 1608, 1514, 1341, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.46 – 6.39 (m, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 5.90 (dd, *J* = 10.7, 5.3 Hz, 1H), 5.28 – 5.20 (m, 2H), 3.82 – 3.75 (m, 2H), 3.11 (dd, *J* = 15.5, 7.8 Hz, 2H), 1.59 – 1.50 (m, 3H), 1.36 – 1.26 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.5, 133.2, 126.1, 118.9, 49.9, 46.1, 30.4, 19.8, 13.7;

HRMS calculated for $C_9H_{18}NO_2S$ $(M+H)^+$ 204.1058, found 204.1066.

***N*-Allyl-N-benzylethenesulfonamide (3.61c)**



Procedure D; Yield 90%;

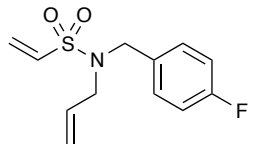
FTIR (neat): 3100, 3069, 1514, 1341, 1286, 1161 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 – 7.27 (m, 5H), 6.47 – 6.41 (m, 1H), 6.27 – 6.21 (m, 1H), 5.93 – 5.89 (m, 1H), 5.81 – 5.71 (m, 1H), 5.20 (dd, *J* = 17.1, 1.2 Hz, 2H), 4.33 (s, 2H), 3.73 (d, *J* = 6.5 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.9, 135.8, 132.2, 128.7, 128.5, 127.9, 126.4, 119.7, 49.6, 48.9;

HRMS calculated for $C_{12}H_{15}NO_2SNa$ $(M+Na)^+$ 260.0721, found 260.0711.

***N*-Allyl-*N*-(4-fluorobenzyl)ethenesulfonamide (3.61d)**



Procedure D; Yield 80%;

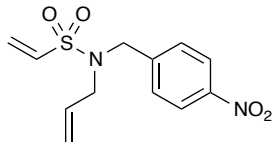
FTIR (neat): 3104, 3066, 1605, 1514, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.28 (m, 2H), 7.06 – 6.99 (m, 2H), 6.46 – 6.39 (m, 1H), 6.27 – 6.21 (m, 1H), 5.96 – 5.90 (m, 1H), 5.74 (ddq, J = 13.1, 10.1, 6.7 Hz, 1H), 5.26 – 5.13 (m, 2H), 4.28 (s, 2H), 3.71 (d, J = 6.6 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.4 (d, $^{1}J_{C\text{-}F}$ = 245.8 Hz), 135.7, 131.6 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz) 131.6, 130.2, (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 126.6, 119.8, 115.5, (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 49.0, 48.9;

HRMS calculated for $C_{12}H_{15}FNO_2S$ $(M+H)^+$ 256.0808, found 256.0809.

***N*-Allyl-*N*-(4-nitrobenzyl)ethenesulfonamide (3.61e)**



Procedure D; Yield 89%;

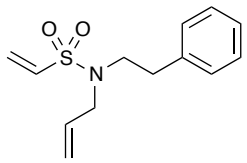
FTIR (neat): 3105, 3069, 1600, 1515, 1286, 1161 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.22 – 8.15 (m, 2H), 7.55 – 7.49 (m, 2H), 6.49 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.30 (dd, *J* = 22.4, 12.3 Hz, 1H), 6.03 – 5.96 (m, 1H), 5.72 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.25 – 5.11 (m, 2H), 4.39 (s, 2H), 3.76 (t, *J* = 9.5 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.6, 143.8, 135.2, 131.8, 128.9, 127.4, 123.8, 120.4, 49.9, 49.3;

HRMS calculated for $C_{12}H_{14}N_2O_4SNa$ $(M+Na)^+$ 283.0753; found 283.0755.

_N_-Allyl-_N_-phenethylethenesulfonamide (3.61f)



Procedure D; Yield 84%;

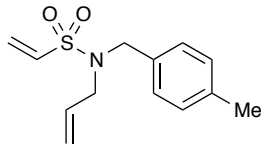
FTIR (neat): 3105, 3069, 1608, 1514, 1340, 1286, 1161 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 6.28 (dd, J = 16.5, 9.5 Hz, 1H), 6.22 – 6.16 (m, 1H), 5.86 (d, J = 9.5 Hz, 1H), 5.84 – 5.74 (m, 1H), 5.29 – 5.23 (m, 2H), 3.79 – 3.77 (m, 2H), 3.37 (dd, J = 8.7, 6.9 Hz, 2H), 2.92 – 2.88 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.4, 135.2, 133.0, 128.9, 128.6, 126.6, 126.2, 119.2, 50.3, 48.3, 35.4;

HRMS calculated for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1053.

***N*-allyl-*N*-(4-methylbenzyl)ethenesulfonamide (3.61g)**



Procedure D; Yield 75%;

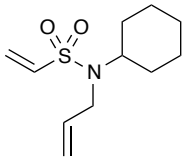
FTIR (neat): 3110, 3070, 1605, 1516, 1347, 1283 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 2H), 6.43 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.25 (d, *J* = 16.6 Hz, 1H), 5.91 (d, *J* = 9.8 Hz, 1H), 5.77 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.29 – 5.14 (m, 2H), 4.30 (s, 2H), 3.72 (dt, *J* = 6.5, 1.3 Hz, 2H), 2.36 (s, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.7, 136.0, 132.7, 132.3, 129.3, 128.6, 126.3, 119.6, 49.4, 48.7, 21.2;

HRMS calculated for $C_{13}H_{18}NO_2S$ $(M+H)^+$ 252.1058, found 252.1060.

***N*-Allyl-*N*-cyclohexylethenesulfonamide (3.61h)**



Procedure D; Yield 88%;

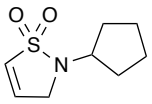
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.35 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.12 (t, *J* = 10.0 Hz, 1H), 5.78 – 5.75 (m, 2H), 5.17 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.07 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.70 (dt, *J* = 6.1, 1.4 Hz, 2H), 3.51 (tt, *J* = 12.3, 3.4 Hz, 1H), 1.76 – 1.68 (m, 4H), 1.58 – 1.52 (m, 1H), 1.46 – 1.35 (m, 2H), 1.29 – 1.16 (m, 2H), 1.04 – 0.93 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 136.6, 136.1, 125.2, 117.2, 57.9, 46.1, 32.2, 26.0, 25.3;

HRMS calculated for $C_{11}H_{20}NO_2S$ $(M+H)^+$ 230.1215, found 230.1210.

2-Cyclopentyl-2,3-dihydroisothiazole 1,1-dioxide (3.62)



Procedure E; Yield 93%;

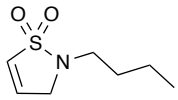
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.82 (tt, *J* = 7.2, 2.1 Hz, 1H), 6.64 – 6.59 (m, 1H), 3.95 (t, *J* = 2.4 Hz, 2H), 3.77 – 3.69 (m, 1H), 2.05 – 1.95 (m, 2H), 1.79 – 1.68 (m, 4H), 1.65 – 1.54 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.9, 127.6, 56.3, 50.4, 30.5, 23.4;

HRMS calculated for $C_8H_{17}N_2O_2S$ $(M+NH_4)^+$ 205.1011, found 205.1012.

2-Butyl-2,3-dihydroisothiazole 1,1-dioxide (3.63)



Procedure E; Yield 98%;

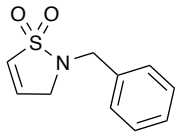
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.85 (dt, *J* = 6.9, 2.4 Hz, 1H), 6.68 – 6.62 (m, 1H), 3.98 – 3.93 (m, 2H), 3.14 (dd, *J* = 15.9, 8.4 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.45 – 1.32 (m, 2H), 0.92 (q, *J* = 7.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.1, 127.5, 52.3, 44.0, 30.1, 19.9, 13.6;

HRMS calculated for $C_7H_{17}N_2O_2S$ $(M+NH_4)^+$ 193.1011, found 193.1018.

2-Benzyl-2,3-dihydroisothiazole 1,1-dioxide (3.64)



Procedure E; Yield 96%;

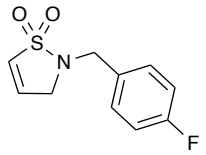
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 (m, 2H), 7.38 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 6.83 (dt, *J* = 7.0, 2.4 Hz, 1H), 6.73 (dt, *J* = 7.0, 2.2 Hz, 1H), 4.37 (s, 2H), 3.83 (t, *J* = 2.3 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.2, 135.1, 128.8, 128.5, 128.2, 127.3, 51.5, 47.5;

HRMS calculated for $C_{10}H_{14}N_2O_2S$ $(M+NH_4)^+$ 227.0854, found 227.0846.

2-(4-Fluorobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.65)



Procedure E; Yield 95%;

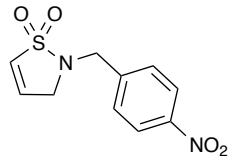
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1116cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.46 – 7.31 (m, 2H), 7.07 – 6.98 (m, 2H), 6.87 – 6.81 (m, 1H), 6.73 – 6.68 (m, 1H), 4.34 – 4.29 (m, 2H), 3.84 – 3.79 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.5 (d, $^{1}J_{C\text{-}F}$ = 245.6 Hz) 135.1, 130.9 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 130.2, (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 127.2, 115.7, (d, $^{2}J_{C\text{-}F}$ = 18.8 Hz), 51.5, 46.9;

HRMS calculated for $C_{10}H_{14}FN_2O_2S$ $(M+NH_4)^+$ 245.0760, found 245.0753.

2-(4-Nitrobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.66)



Procedure E; Yield 98%;

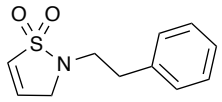
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.24 – 8.19 (m, 2H), 7.63 – 7.56 (m, 2H), 6.92 – 6.87 (m, 1H), 6.78 (dt, *J* = 7.0, 2.3 Hz, 1H), 4.46 (d, *J* = 12.9 Hz, 2H), 3.95 – 3.88 (s, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.8, 142.9, 134.9, 129.1, 127.2, 124.1, 51.9, 47;

HRMS calculated for $C_{10}H_{14}N_3O_4S$ $(M+NH_4)^+$ 272.0705, found 272.0699.

2-Phenethyl-2,3-dihydroisothiazole 1,1-dioxide (3.67)



Procedure E; Yield 96%;

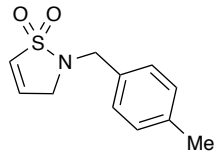
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 (dd, *J* = 10.3, 5.0 Hz, 2H), 7.24 (dd, *J* = 13.0, 7.0 Hz, 3H), 6.82 – 6.78 (m, 1H), 6.64 (dt, *J* = 14.0, 7.1 Hz, 1H), 3.91 – 3.84 (m, 2H), 3.49 – 3.42 (m, 2H), 2.99 (dd, *J* = 15.6, 8.4 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 138.4, 135.3, 128.8, 128.7, 127.3, 126.7, 52.9, 45.8, 35.1;

HRMS calculated for $C_{11}H_{14}NO_2S$ $(M+H)^+$ 224.0754, found 224.0753.

2-(4-Methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.68)



Procedure E; Yield 93%;

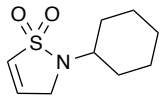
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.19 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.75 (dt, *J* = 7.0, 2.4 Hz, 1H), 6.63 (dt, *J* = 7.0, 2.2 Hz, 1H), 4.23 (s, 2H), 3.73 (t, *J* = 2.3 Hz, 2H), 2.27 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 135.1, 131.9, 129.5, 128.5, 127.3, 51.4, 47.3, 21.2;

HRMS calculated for $C_{11}H_{17}N_2O_2S$ $(M+NH_4)^+$ 241.1106, found 241.1006.

2-Cyclohexyl-2,3-dihydroisothiazole 1,1-dioxide (3.69)



Procedure E; Yield 92%;

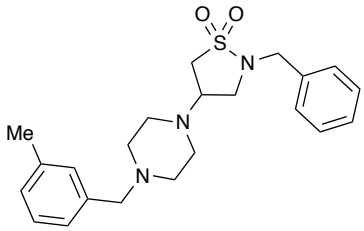
FTIR (neat): 3105, 3078, 1606, 1517, 1344, 1286, 1161 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.87 – 6.82 (m, 1H), 6.62 (dt, *J* = 7.0, 2.3 Hz, 1H), 3.99 (t, *J* = 2.3 Hz, 2H), 3.52 (tt, *J* = 11.4, 3.7 Hz, 1H), 2.04 – 1.96 (m, 2H), 1.81 (ddd, *J* = 6.1, 3.4, 1.0 Hz, 2H), 1.68 – 1.60 (m, 1H), 1.49 (ddd, *J* = 23.8, 12.3, 3.3 Hz, 2H), 1.41 – 1.29 (m, 2H), 1.19 – 1.06 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.6, 127.5, 52.9, 47.5, 31.3, 25.4, 25.4;

HRMS calculated for $C_9H_{16}NO_2S$ $(M+H)^+$ 202.0902, found 202.0907.

2-Benzyl-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 3.64{4}



Procedure F;

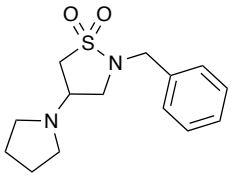
FTIR (neat): 2962, 2806, 1454, 1305, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 – 7.30 (m, 5H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 14.9, 7.3 Hz, 3H), 4.16 (q, *J* = 14.1 Hz, 2H), 3.55 – 3.47 (m, 1H), 3.44 (s, 2H), 3.35 (dd, *J* = 12.8, 8.3 Hz, 1H), 3.25 – 3.17 (m, 2H), 2.98 (dd, *J* = 9.5, 7.2 Hz, 1H), 2.45 (s, 8H), 2.33 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 137.6, 135.1, 129.7, 128.7, 128.6, 128.2, 128.1, 127.9, 126.3, 62.9, 56.9, 52.7, 49.6, 49.1, 48.2, 47.6, 21.4;

HRMS calculated for $C_{22}H_{30}N_3O_2S$ $(M+H)^+$ 400.2059, found 400.2070.

2-Benzyl-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.64{16}



Procedure F;

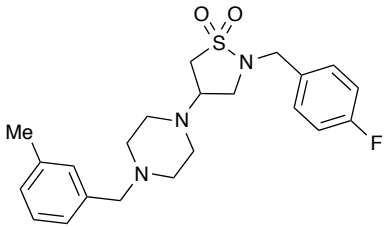
FTIR (neat): 2962, 2805, 1450, 1305, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.22 (m, 5H), 4.20 (d, *J* = 14.3 Hz, 1H), 4.05 (t, *J* = 14.3 Hz, 1H), 3.38 – 3.29 (m, 2H), 3.19 – 3.09 (m, 2H), 2.96 – 2.90 (m, 1H), 2.46 – 2.35 (m, 4H), 1.73 – 1.64 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.3, 128.7, 128.5, 128.0, 56.1, 51.3, 50.9, 50.8, 47.7, 23.2;

HRMS calculated for $C_{14}H_{21}N_2O_2S$ $(M+H)^+$ 281.1324, found 281.1321.

2-(4-Fluorobenzyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 3.65{4}



Procedure F;

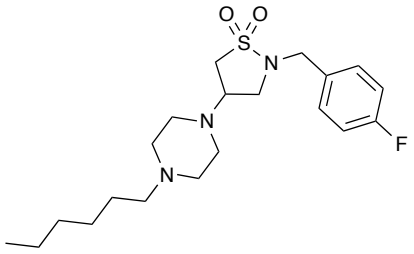
FTIR (neat): 2943, 2813, 1510, 1307, 1222, 1139 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.28 (m, 2H), 7.19 (dd, *J* = 13.1, 5.5 Hz, 1H), 7.07 (dd, *J* = 13.2, 5.7 Hz, 3H), 7.05 – 7.01 (m, 2H), 4.13 (q, *J* = 14.2 Hz, 2H), 3.51 (p, *J* = 8.0 Hz, 1H), 3.44 (s, 2H), 3.34 (dd, *J* = 12.8, 8.3 Hz, 1H), 3.20 (ddd, *J* = 15.4, 11.1, 7.9 Hz, 2H), 2.97 (dd, *J* = 9.5, 7.2 Hz, 1H), 2.45 (s, 8H), 2.33 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.4 (d, $^{1}J_{C\text{-}F}$ = 246.7 Hz), 137.9, 137.5, 130.8 (d, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 130.3 (d, $^{2}J_{C\text{-}F}$ = 9.2 Hz), 129.8, 128.1, 127.9, 126.3, 115.7 (d, $^{2}J_{C\text{-}F}$ = 25.0 Hz), 62.9, 56.9, 52.7, 49.6, 49.0, 48.2, 46.9, 21.4;

HRMS calculated for $C_{22}H_{29}FN_3O_2S$ $(M+H)^+$ 418.1965, found 418.1968.

2-(4-Fluorobenzyl)-4-(4-hexylpiperazin-1-yl)isothiazolidine 1,1-dioxide 3.65{7}



Procedure F;

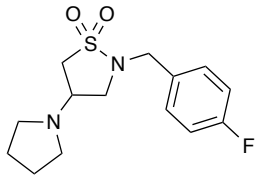
FTIR (neat): 2966, 2806, 1510, 1307, 1220, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 – 7.28 (m, 2H), 7.05 – 7.01 (m, 2H), 4.19 – 4.07 (m, 2H), 3.50 (p, J = 8.0 Hz, 1H), 3.35 (dd, J = 12.8, 8.3 Hz, 1H), 3.19 (ddd, J = 13.9, 11.1, 7.9 Hz, 2H), 2.97 (dd, J = 9.5, 7.2 Hz, 1H), 2.45 (s, 8H), 2.28 (dd, J = 8.9, 6.7 Hz, 2H), 1.48 – 1.38 (m, 2H), 1.31 – 1.22 (m, 6H), 0.86 (t, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.5 (d, $^{1}J_{C\text{-}F}$ = 249.9 Hz), 130.8 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz), 130.3 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 58.6, 56.9, 52.8, 49.7, 48.9, 48.3, 46.9, 31.7, 27.2, 26.8, 22.6, 14.0;

HRMS calculated for $C_{20}H_{33}FN_3O_2S$ $(M+H)^+$ 398.2278, found 398.2284.

2-(4-Fluorobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.65{16}



Procedure F;

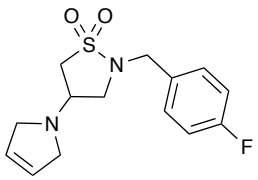
FTIR (neat): 2964, 2806, 1510, 1307, 1222, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 – 7.30 (m, 2H), 7.06 – 7.01 (m, 2H), 4.23 (d, J = 14.3 Hz, 1H), 4.08 (d, J = 14.3 Hz, 1H), 3.44 – 3.35 (m, 2H), 3.23 – 3.17 (m, 2H), 3.01 – 2.95 (m, 1H), 2.52 – 2.42 (m, 4H), 1.79 – 1.74 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.5 (d, $^{1}J_{C\text{-}F}$ = 243.5 Hz), 131.0 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 130.3 (d, $^{3}J_{C\text{-}F}$ = 10.2 Hz), 115.7 (d, $^{1}J_{C\text{-}F}$ = 21.7 Hz), 56.1, 51.3, 50.9, 50.9, 47.1, 23.2;

HRMS calculated for $C_{14}H_{20}FN_2O_2S$ $(M+H)^+$ 299.1230, found 299.1234.

4-(2,5-Dihydro-1*H*-pyrrol-1-yl)-2-(4-fluorobenzyl)isothiazolidine 1,1-dioxide 3.65{17}



Procedure F;

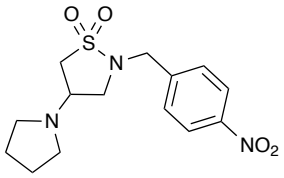
FTIR (neat): 2964, 2808, 1510, 1304, 1222, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 – 7.30 (m, 2H), 7.06 – 7.01 (m, 2H), 5.77 – 5.74 (m, 2H), 4.22 (d, J = 14.3 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.74 (p, J = 7.6 Hz, 1H), 3.53 – 3.38 (m, 5H), 3.21 (ddd, J = 17.5, 11.1, 7.5 Hz, 2H), 2.98 (dd, J = 9.4, 7.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 162.5 (d, $^{1}J_{C\text{-}F}$ = 258.6 Hz), 131.0 (d, $^{4}J_{C\text{-}F}$ = 2.97 Hz), 130.3 (d, $^{2}J_{C\text{-}F}$ = 9.52 Hz), 127.2, 115.7 (d, $^{1}J_{C\text{-}F}$ = 22.0 Hz), 56.8, 55.4, 50.5, 50.3, 47.0;

HRMS calculated for $C_{14}H_{18}FN_2O_2S$ $(M+H)^+$ 297.1073, found 297.1072.

2-(4-Nitrobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.66{16}



Procedure F;

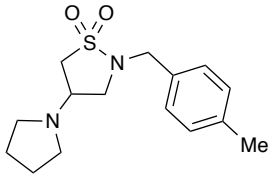
FTIR (neat): 2962, 2358, 1519, 1346, 1305, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.24 – 8.19 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 4.38 (d, *J* = 15.3 Hz, 1H), 4.20 (d, *J* = 15.3 Hz, 1H), 3.48 – 3.40 (m, 2H), 3.29 – 3.20 (m, 2H), 3.05 (dt, *J* = 8.9, 6.2 Hz, 1H), 2.49 (dt, *J* = 9.2, 6.7 Hz, 4H), 1.81 – 1.74 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.7, 143.0, 129.1, 124.0, 56.2, 51.5, 51.4, 50.8, 47.4, 23.2;

HRMS calculated for $C_{14}H_{20}N_3O_4S$ $(M+H)^+$ 326.1175, found 326.1178.

2-(4-Methylbenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.68{16}



Procedure F;

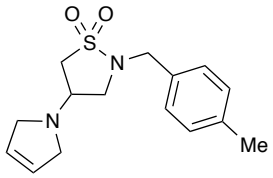
FTIR (neat): 2962, 1305, 1236, 1141 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.16 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.14 (t, *J* = 12.5 Hz, 1H), 3.99 (d, *J* = 14.1 Hz, 1H), 3.32 (tdd, *J* = 21.2, 13.4, 7.7 Hz, 2H), 3.17 – 3.09 (m, 2H), 2.91 (ddd, *J* = 13.1, 6.5, 3.5 Hz, 1H), 2.45 – 2.34 (m, 4H), 2.27 (s, 3H), 1.74 – 1.64 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.7, 132.2, 129.4, 128.5, 56.1, 51.3, 50.9, 50.8, 47.4, 23.2, 21.2;

HRMS calculated for $C_{15}H_{23}N_2O_2S$ $(M+H)^+$ 295.1480, found 295.1480.

4-(2,5-Dihydro-1*H*-pyrrol-1-yl)-2-(4-methylbenzyl)isothiazolidine 1,1-dioxide 3.68{17}



Procedure F;

FTIR (neat): 2968, 1305, 1236, 1141 cm^{-1};

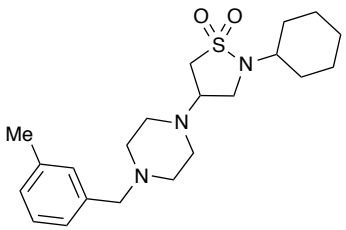
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.75 (d, *J* = 7.2 Hz, 2H), 4.24 – 4.19 (m, 1H), 4.10 – 4.05 (m, 1H), 3.77 – 3.69 (m, 1H), 3.51 – 3.38 (m, 5H), 3.25 – 3.16 (m, 2H), 2.98 (dd, *J* = 9.5, 7.3 Hz, 1H), 2.35 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.8, 132.1, 129.4, 128.5, 127.2, 56.8, 55.4, 50.4, 50.3, 47.4, 21.2;

HRMS calculated for $C_{15}H_{21}N_2O_2S$ $(M+H)^+$ 293.1323, found 293.1329.

2-Cyclohexyl-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide

3.69{4}



Procedure F;

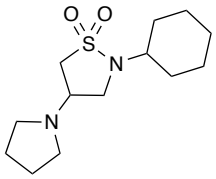
FTIR (neat): 2930, 2856, 1450, 1297, 1236, 1134 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.20 (t, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 18.1, 9.0 Hz, 3H), 3.53 – 3.42 (m, 4H), 3.39 (dd, *J* = 9.0, 7.4 Hz, 1H), 3.27 (dd, *J* = 12.6, 8.1 Hz, 1H), 3.13 (dt, *J* = 12.4, 7.8 Hz, 2H), 2.49 (d, *J* = 30.0 Hz, 8H), 2.34 (s, 3H), 1.95 – 1.87 (m, 2H), 1.78 (d, *J* = 13.0 Hz, 2H), 1.66 – 1.59 (m, 1H), 1.36 (m, 4H), 1.13 – 1.02 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 137.9, 129.9, 128.2, 127.9, 126.3, 62.9, 57.2, 52.8, 52.7, 49.7, 49.2, 44.7, 31.2, 30.9, 25.5, 25.4, 21.4;

HRMS calculated for $C_{21}H_{34}N_3O_2S$ $(M+H)^+$ 392.2372, found 392.2408

2-Cyclohexyl-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.69{16}



Procedure F;

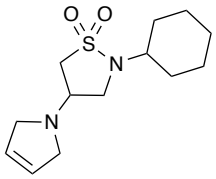
FTIR (neat): 2933, 2856, 1450, 1296, 1236, 1132 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.47 – 3.36 (m, 3H), 3.36 – 3.29 (m, 1H), 3.16 – 3.07 (m, 2H), 2.59 – 2.47 (m, 4H), 1.91 (dd, *J* = 20.3, 9.2 Hz, 2H), 1.82 – 1.74 (m, 6H), 1.66 – 1.59 (m, 1H), 1.48 – 1.26 (m, 4H), 1.08 (q, *J* = 12.7, 3.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 56.4, 52.9, 51.6, 51.4, 46.6, 31.3, 30.8, 25.5, 25.4, 23.3;

HRMS calculated for $C_{13}H_{25}N_2O_2S$ $(M+H)^+$ 273.1636, found 273.1641.

2-Cyclohexyl-4-(2,5-dihydro-1*H*-pyrrol-1-yl)isothiazolidine 1,1-dioxide 3.69{17}



Procedure F;

FTIR (neat): 2930, 2852, 1451, 1296, 1236, 1131 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.79 (s, 2H), 3.76 – 3.68 (m, 1H), 3.58 – 3.46 (m, 4H), 3.43 (ddd, *J* = 16.2, 8.4, 5.4 Hz, 2H), 3.32 (dd, *J* = 12.6, 7.9 Hz, 1H), 3.11 (ddd, *J* = 19.8, 10.8, 8.0 Hz, 2H), 1.91 (ddd, *J* = 12.3, 10.6, 3.3 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.66 – 1.59 (m, 1H), 1.48 – 1.27 (m, 4H), 1.08 (qt, *J* = 12.7, 3.6 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 127.3, 56.9, 55.7, 52.9, 50.9, 46.3, 31.3, 30.8, 25.5, 25.4, 25.3;

HRMS calculated for $C_{13}H_{22}N_2O_2SNa$ $(M+Na)^+$ 293.1323, found 293.1327.

Purification results of 144 member library

Compound	Expected Mass	Found Mass	Yield (%)	Final Purity (%)
3.62{1}	288.1745	288.1775	8	100
3.62{2}	318.1851	318.1887	40	100
3.62{3}	345.2323	345.2335	37	100
3.62{4}	378.2215	378.2242	48	100
3.62{8}	368.1635	368.1660	35	100
3.62{9}	371.2480	371.2491	20	100
3.62{10}	328.2058	328.2077	46	100
3.62{12}	363.2105	363.2111	45	100
3.62{15}	290.1901	290.1902	28	100
3.62{16}	259.1479	259.1484	44	100
3.63{1}	276.1745	276.1758	39	100
3.63{2}	306.1851	306.1864	37	100
3.63{3}	333.2323	333.2353	36	100
3.63{4}	366.2214	366.2218	45	100
3.63{7}	346.2527	346.2542	36	100
3.63{8}	356.1644	356.1652	20	100
3.63{9}	359.2480	359.2484	22	100
3.63{10}			Sample Lost	
3.63{11}	261.1636	261.1649	19	100
3.63{12}	351.2106	351.2155	15	100
3.63{15}	278.1901	278.1906	26	100
3.63{16}	247.1479	247.1492	37	100
3.63{17}	245.1323	245.1339	31	87
3.64{1}	310.1589	310.1603	38	100
3.64{2}	340.1694	340.1711	40	100

3.64{3}	367.2167	367.2186	28	100
3.64{4}	400.2058	400.2070	47	100
3.64{5}	373.1697	373.1700	22	99
3.64{6}			Sample Lost	
3.64{7}	380.2371	380.2405	37	98
3.64{8}	390.1487	390.1512	35	100
3.64{9}	393.2323	393.2333	14	100
3.64{10}	350.1901	350.1905	45	100
3.64{11}	295.1479	295.1499	55	99
3.64{12}	385.1949	385.1961	49	96
3.64{13}	371.1792	371.1812	43	98
3.64{14}	353.1534	353.1546	43	100
3.64{15}	312.1745	312.1697	33	98
3.64{16}	281.1132	281.1281	44	100
3.64{17}	279.1166	279.1126	52	91
3.65{1}	328.1494	328.1497	36	100
3.65{2}	358.1600	358.1604	50	91
3.65{3}	385.2073	385.2076	47	96
3.65{4}	418.1964	418.1966	46	100
3.65{5}	391.1603	391.1600	43	91
3.65{6}	392.1556	392.1558	47	100
3.65{7}	398.2277	398.2278	51	98
3.65{8}	408.1393	408.1388	46	98
3.65{9}	411.2229	411.2231	35	100
3.65{10}	3681807	368.1811	49	99
3.65{11}	313.1385	313.1386	50	100
3.65{12}	403.1855	403.1858	42	100
3.65{13}	389.1699	389.1703	53	99

3.65{14}	371.1440	371.1441	51	99
3.65{15}	330.1651	330.1653	35	100
3.65{16}	299.1229	229.1234	46	99
3.65{17}	297.1072	297.1072	40	91
3.66{1}	355.1439	355.1442	40	99
3.66{2}	385.1545	385.1543	45	100
3.66{3}	412.2018	412.2019	18	93
3.66{4}	445.1909	445.1906	52	100
3.66{7}	425.2222	425.2225	50	100
3.66{8}	435.1338	435.1333	40	96
3.66{9}	438.2174	438.2173	50	96
3.66{10}	395.1752	395.1754	46	99
3.66{11}	340.1330	340.1327	70	100
3.66{12}	430.1800	430.1797	50	99
3.66{13}	416.1643	416.1646	56	100
3.66{14}	398.1385	398.1382	83	98
3.66{15}	357.1596	357.1598	32	96
3.66{16}	326.1174	326.1176	48	100
3.66{17}	324.1017	324.1013	50	96
3.67{1}	324.1745	324.1749	49	99
3.67{2}	354.1851	354.1854	56	100
3.67{3}	381.2323	381.2324	33	96
3.67{4}	414.2214	414.2218	46	100
3.67{7}	394.2527	394.2528	50	100
3.67{8}	404.1643	404.1643	38	90
3.67{9}	407.2480	407.2483	28	100
3.67{10}	364.2058	364.2061	52	99
3.67{11}	309.1636	309.1637	51	100
3.67{12}	399.2105	399.2106	50	100

3.67{15}	326.1901	326.1905	36	100
3.67{16}	295.1479	295.1482	46	99
3.67{17}	293.1323	293.1327	44	89
3.68{1}	324.1745	324.1765	40	100
3.68{2}	354.1851	354.1864	52	100
3.68{3}	381.2323	381.2313	5	100
3.68{4}	414.2215	414.2222	52	100
3.68{5}	387.1854	387.1872	52	99
3.68{7}	394.2527	394.2498	54	100
3.68{9}	407.2480	407.2472	35	100
3.68{10}	364.2058	364.2080	54	98
3.68{11}	309.1636	309.1641	55	100
3.68{12}	399.2105	399.2096	53	93
3.68{13}	385.1949	385.1961	58	99
3.68{14}	367.1691	367.1719	57	98
3.68{15}	326.1901	326.1933	2	100
3.68{16}	295.1479	295.1506	60	99
3.68{17}	293.1323	293.1329	47	97
3.69{1}	302.1901	302.1912	48	100
3.69{2}	332.2007	332.2004	51	92
3.69{3}	359.2480	359.2497	16	100
3.69{4}	392.2371	392.2408	48	99
3.69{5}	365.2010	365.2017	43	100
3.69{7}	372.2684	372.2688	54	100
3.69{8}	382.1800	382.1860	22	99
3.69{9}	385.2636	385.2644	23	100
3.69{10}	342.2214	342.2231	45	100
3.69{11}	287.1792	287.1787	53	100
3.69{12}	377.2262	377.2288	56	100

3.69{13}	363.2105	363.2101	61	100
3.69{14}	345.1847	345.1880	50	93
3.69{15}			Sample Lost	
3.69{16}	273.1636	273.1641	53	100
3.69{17}	271.1479	271.1490	45	100
(***R***)-**3.3**{1}	340.1694	340.1720	20	100
(***R***)-**3.3**{2}	370.1800	370.1821	30	100
(***R***)-**3.3**{3}	367.2273	397.2275	10	100
(***R***)-**3.3**{4}	430.2164	430.2155	25	96
(***R***)-**3.3**{5}	403.1803	403.1800	23	95
(***R***)-**3.3**{7}	410.2477	410.2478	5	100
(***R***)-**3.3**{10}	380.2007	380.2029	15	100
(***R***)-**3.3**{12}	415.2055	415.2054	41	99
(***R***)-**3.3**{16}	311.1429	311.1428	50	99
(***R***)-**3.3**{18}	325.1585	325.1611	25	100
(***R***)-**3.3**{19}	327.1378	327.1403	53	100
(***R***)-**3.3**{20}	355.1691	355.1685	19	97
(***R***)-**3.3**{21}	355.1691	355.1706	8	100
(***R***)-**3.3**{22}	341.1534	341.1550	9	95
(***R***)-**3.3**{23}	354.1851	354.1869	19	100
(***S***)-**3.3**{1}	340.1695	340.1719	8	100
(***S***)-**3.3**{2}	370.1800	370.1811	28	96
(***S***)-**3.3**{3}	397.2273	397.2290	11	95
(***S***)-**3.3**{4}	430.2164	430.2154	20	95
(***S***)-**3.3**{10}	380.2007	380.2042	20	97
(***S***)-**3.3**{12}	415.2055	415.2068	26	100
(***S***)-**3.3**{16}	311.1429	311.1453	47	100
(***S***)-**3.3**{18}	325.1585	325.1593	15	100

(*S*)-3.3{19}	327.1378	327.1395	47	99
(*S*)-3.3{20}	355.1691	355.1722	7	100
(*S*)-3.3{21}	355.1691	355.1722	19	96
(*S*)-3.3{22}	341.1534	341.1541	19	100
(*S*)-3.3{23}	354.1851	354.1852	18	100

5.4 Experimental Data for Chapter 4

General procedure for preparation of tertiary 2-bromobenzenesulfonamides

To an r. b. flask containing a solution of primary amine (2.2 mmol, 1.1 eq) in dry CH_2Cl_2 (0.1 M), was added Et_3N (3.9 mmol, 2.0 eq). The reaction mixture was cooled to 0 ºC, stirred for 5 minutes, after which benzenesulfonyl chloride (2.0 mmol, 1.0 eq) was added to the reaction mixture, warmed to rt for 12 h. The reaction was quenched with water, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired secondary 2-bromobenzenesulfonamide.

The crude secondary 2-bromobenzenesulfonamide (2.4 mmol, 1 eq) was added to a flame-dried flask, to which Cs_2CO_3 (4.1 mmol, 1.2 eq) and dry CH_3CN (0.2 M) were added. After stirring for 5 min, propargyl bromide (4.1 mmol, 1.2 eq) was added and the reaction mixture was stirred at 60 ºC until completion of reaction (as monitored by TLC). The crude reaction mixture was filtered through a pad of Celite, washed with CH_2Cl_2, concentrated under reduced pressure to furnish the desired product.

General procedure for Huisgen's 1,3-dipolar [3+2] cycloaddition reaction

To a flame dried r. b. flask charged with alkynyl-sulfonamide (1.4 mmol, 1 eq) was added ^{t}BuOH:CH_2Cl_2 (2.3 mL: 2.3 mL, 1:1). Benzyl azide (2.8 mmol, 2 eq) was added. To another flame dried round bottom flask $CuSO_4$•$5H_2O$ (0.3 mmol, 0.2 eq) and (+)-sodium *L*-ascorbate (0.4 mmol, 0.3 eq) were added in H_2O (2.3 mL) and the resulting solution was added into the previous flask. The reaction mixture was stirred

at rt for 12 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (1:1 hexane:EtOAc) to yield the desired product.

General procedure for Mitsunobu reaction

A portion of the secondary benzenesulfonamide (2.5 mmol, 1 eq) was added to a flame-dried flask under argon, to which were added PPh_3 (5.3 mmol, 2 eq) and dry CH_2Cl_2 (0.5 M). After stirring for 5 min at 0 ºC, 3-butyn-1-ol (5.3 mmol, 2 equiv) was added followed by dropwise addition of diisopropyl azodicarboxylate (DIAD) (5.3 mmol, 2 eq) at 0 ºC. The reaction mixture was stirred at rt for 12 h, after which time the crude mixture was concentrated under reduced pressure and purified by flash chromatography (5:1 hexane:EtOAc) to obtain the desired product.

General procedure for *C*-arylation reaction (method A)

To an oven dried seal vial were added 1,2,3-triazole containing 2-bromobenzenesulfonamide (0.34 mmol, 1 eq), $Pd(OAc)_2$ (0.034 mmol, 10 mol%), and tetrabutylammonium acetate (0.683 mmol, 2 eq) under N_2 atmosphere. *N*-Methylpyrrolidone (0.5 M) was then added, and the reaction mixture was stirred at 110 °C for 17 h monitoring by TLC. The reaction mixture was diluted with EtOAc (20 mL), washed twice with 10 mL portions of water and brine, dried over anhydrous Na_2SO_4. The solvents were removed and the residue was purified via flash chromatography (1:1 hexane:EtOAc) to afford tricyclic sultam compounds.

General procedure for *C*-arylation reaction (method B)

To an oven dried seal vial were added 1,2,3-triazole containing 2-bromobenzenesulfonamide (0.34 mmol, 1 eq), $Pd(PPh_3)_4$ (0.034 mmol, 10 mol%), and KOAc (0.683 mmol, 2 eq) under N_2 atmosphere. Anhydrous DMF (0.5 M) was then added, and the reaction mixture was stirred at 110 °C for 17 h monitoring by TLC. The reaction mixture was diluted with EtOAc (20 mL), washed twice with 10 mL portions of water and brine, dried over anhydrous Na_2SO_4. The solvents were removed and the residue was purified via flash chromatography (1:1 hexane:EtOAc) to afford tricyclic sultam compounds.

General procedure for preparation of azides

Caution: While synthesis of azides has become ubiquitous in the literature some are explosive and care should be taken when synthesizing and handling them.

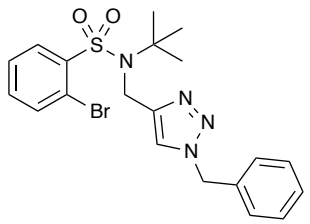
To a stirred solution of the corresponding bromide (1.0 eq) in anhydrous DMF (1 M) was added NaN_3 (2 eq). The resulting suspension was stirred at room temperature for 15 h. Diethyl ether and water were added to the mixture and the organic layer was separated. The organic layer was washed with water (4 × 20 mL) and the organic layers was dried over Na_2SO_4. Solvent was removed under reduced pressure, and the azide was sufficiently pure to use without further work up.

General procedure for preparation of phenyl azide

A mixture of aniline 1 mL (10.97 mmol), water (15.7 mL), and concd HCl (15.7 mL) was stirred at 0–5 °C for 30 min. The amine hydrochloride was then deazotized by the dropwise addition of aq $NaNO_2$ (0.9 g, 13.04 mmol, in 13.2 mL H_2O). The solution

was stirred at 0–5 °C and treated with aq NaN_3 (1.42 g, 21.85 mmol, in 13.2 mL H_2O). After stirring for 1 h at 0–5 ºC, the reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the azide as a yellow oil.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-(*tert* butyl)benzenesulfonamide (4.16)**



Yield 66%; Mp 135 ºC;

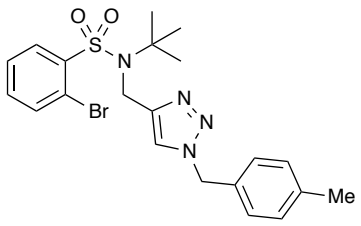
FTIR (neat): 2987, 1319, 1101, 912 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.82 (s, 1H), 7.74 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 – 7.33 (m, 4H), 7.26 (dd, *J* = 7.7, 2.3 Hz, 2H), 5.56 (s, 2H), 5.00 (s, 2H), 1.26 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.8, 143.4, 135.5, 134.8, 133.0, 131.3, 129.0, 128.6, 127.8, 127.6, 124.0, 119.8, 60.1, 54.2, 43.0, 30,1;

HRMS calculated for $C_{20}H_{24}BrN_4O_2S$ $(M+H)^+$ 463.0803, found 463.0792.

2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.17)



Yield 71%;

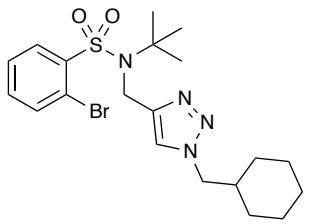
FTIR (neat): 2985, 1326, 1153, 907 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H) 7.77 (s, 1H), 7.72 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.43 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 (td, *J* = 7.7, 1.8 Hz, 7 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 2H), 4.97 (s, 2H), 2.35 (s, 3H), 1.27 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.8, 143.4, 135.5, 134.8, 133.0, 131.3, 129.0, 128.6, 127.8, 127.6, 124.0, 119.8, 60.1, 54.2, 43.0, 30,1, 21.1;

HRMS calculated for $C_{21}H_{26}BrN_4O_2S$ $(M+H)^+$ 477.0960, found 477.0942.

2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.18)



Yield 68%;

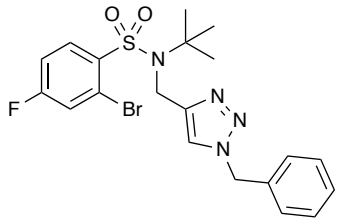
FTIR (neat): 3143, 2975, 2925, 1448, 1323, 1126 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H) 7.80 (s, 1H), 7.82 (s, 1H), 7.75 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.38 (td, *J* = 7.7, 1.7 Hz, 1H), 5.00 (s, 2H), 4.18 (d, *J* = 7.2 Hz, 2H) 1.93 – 1.88 (m, 1H) 1.75 – 1.59 (m, 5H) 1.27 (s, 9H) 1.22 – 1.14 (m, 2H) 1.04 – 0.96 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.1, 143.4, 135.5, 133.0, 131.3, 127.6, 124,3, 119.9, 60.1, 56.6, 43.1, 38.7, 30.4, 30.1, 26.1, 25.5;

HRMS calculated for $C_{20}H_{30}BrN_4O_2S$ $(M+H)^+$ 469.1273, found 469.1185.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-(*tert*-butyl)-4-fluorobenzenesulfonamide (4.19)**



Yield 77%;

Mp 150 ºC;

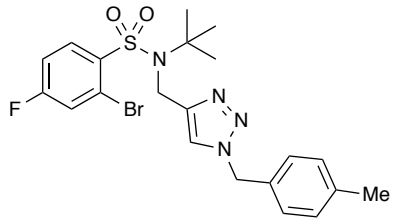
FTIR (neat): 2978, 1583, 1466, 1325, 1150 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (dd, J = 8.9 Hz, $^{4}J_{H-F}$ = 5.8 Hz, 1H), 7.78 (s, 1H), 7.45 (dd, J = 2.6 Hz, $^{3}J_{H-F}$ = 8.0 Hz, 1H), 7.39 – 7.32 (m, 3H), 7.26 – 7.22 (m, 2H), 7.12 (ddd, J = 9.4, 2.4 Hz, $^{3}J_{H-F}$ = 7.5 Hz, 1H), 5.54 (s, 2H), 4.97 (s, 2H), 1.27 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.7 (d, $^{1}J_{C-F}$ = 259.1 Hz), 147.5, 139.7 (d, $^{4}J_{C-F}$ = 3.7 Hz), 134.8, 133.3 (d, $^{3}J_{C-F}$ = 10.1 Hz), 129.0, 128.6, 127.8, 124.0, 122.7 (d, $^{2}J_{C-F}$ = 25.2 Hz), 121.0, (d, $^{3}J_{C-F}$ = 10.1 Hz), 114.8 (d, $^{2}J_{C-F}$ = 21.4 Hz), 60.2, 54.2, 43.0, 30.1;

HRMS calculated for $C_{20}H_{23}BrFN_4O_2S$ $(M+H)^+$ 481.0709, found 481.0706.

2-Bromo-*N*-(*tert*-butyl)-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.20)



Yield 87%;

Mp 140 ºC;

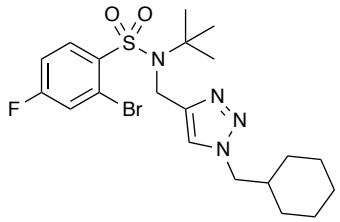
FTIR (neat): 2977, 1583, 1325, 1150 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (dd, J = 8.9 Hz, $^{4}J_{H-F}$ = 5.8 Hz, 1H), 7.75 (s, 1H), 7.45 (dd, J = 2.5 Hz, $^{3}J_{H-F}$ = 8.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.12, (ddd, J = 9.0, 2.6 Hz, $^{3}J_{H-F}$ = 7.5 Hz, 1H), 5.49 (s, 2H), 4.96 (s, 2H), 2.35 (s, 3H), 1.27 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.7 (d, $^{1}J_{C-F}$ = 257.8 Hz), 147.4, 139.7 (d, $^{4}J_{C-F}$ = 3.7 Hz), 138.5, 133.3 (d, $^{3}J_{C-F}$ = 8.8 Hz), 131.7, 129.7, 127.8, 123.9, 122.7 (d, $^{2}J_{C-F}$ = 25.2 Hz), 121.0, (d, $^{3}J_{C-F}$ = 10.1 Hz), 114.8 (d, $^{2}J_{C-F}$ = 20.1 Hz), 60.2, 54.0, 43.0, 30.1, 21.1;

HRMS calculated for $C_{21}H_{25}BrFN_4O_2S$ $(M+H)^+$ 495.0866, found 495.0851.

2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorobenzenesulfonamide (4.21)



Yield 83%;

Mp 124 ºC;

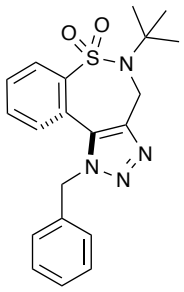
FTIR (neat): 2926, 1734, 1583, 1464, 1325, 1150 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J = 9.0 Hz, $^{4}J_{H\text{-}F}$ = 5.8 Hz, 1H), 7.78 (s, 1H), 7.48 (dd, J = 2.6 Hz, $^{3}J_{H\text{-}F}$ = 8.0 Hz, 1H), 7.15 (ddd, J = 9.0, 2.6 Hz, $^{3}J_{H\text{-}F}$ = 7.4 Hz, 1H), 4.99 (s, 2H), 4.18 (d, J = 7.2 Hz, 2H), 1.90 (m, 1H), 1.75 – 1.59 (m, 5H), 1.27 (s, 9H), 1.25 – 1.10 (m, 3H), 1.03 – 0.94 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.8 (d, $^{1}J_{C\text{-}F}$ = 259.1 Hz), 146.9, 139.8 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 133.3 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 124.3, 122.7 (d, $^{2}J_{C\text{-}F}$ = 23.9 Hz), 121.1 (d, $^{3}J_{C\text{-}F}$ = 10.1 Hz), 114.8 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 60.2, 56.6, 43.1, 38.7, 30.4, 30.1, 26.1, 25.5;

HRMS calculated for $C_{20}H_{29}BrFN_4O_2S$ $(M+H)^+$ 487.1179, found 487.1159.

(±)-1-Benzyl-5-(*tert*-butyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.22)



Yield 99%;

Mp 156 ºC;

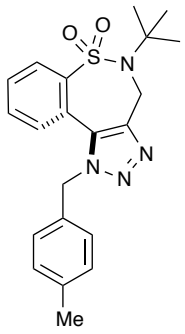
FTIR (neat): 2979, 1340, 1163, 912 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dd, *J* = 7.4, 1.5 Hz, 1H) 7.51 – 7.44 (m, 3H) 7.41 – 7.31 (m, 3H) 7.22 (dd, *J* = 8.2, 1.4 Hz, 2H), 5.71 (s, 2H), 5.03 (s, 2H), 1.18 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.4, 142.9, 135.3, 132.1, 131.4, 129.2, 129.1, 128.7, 128.7, 128.3, 126.5, 124.3, 59.6, 53.4, 44.7, 29.0;

HRMS calculated for $C_{20}H_{23}N_4O_2S$ $(M+H)^+$ 383.1589, found 383.1526.

(±)-5-(*tert*-Butyl)-1-(4-methylbenzyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.23)



Yield 78%;

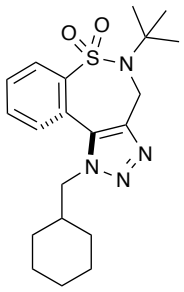
FTIR (neat): 2977, 1342, 1163, 912 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 5.65 (s, 2H), 5.02 (s, 2H), 2.35 (s, 3H), 1.17 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.3, 142.8, 138.1, 132.3, 132.1, 131.3, 129.8, 129.2, 128.6, 126.5, 124.3, 59.6, 53.3, 44.7, 29.0, 21.1;

HRMS calculated for $C_{21}H_{25}N_4O_2S$ $(M+H)^+$ 397.1746, found 397.1672.

(±)-5-(*tert*-Butyl)-1-(cyclohexylmethyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.24)



Yield 84%;

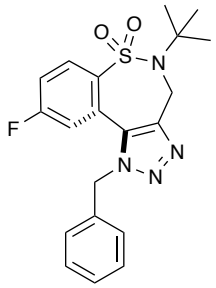
FTIR (neat): 2975, 2927, 1479, 1342, 1190 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 (td, *J* = 7.7, 1.4 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.53 (td, *J* = 7.7, 1.3 Hz, 1H), 4.98 (s, 2H), 4.39 (d, *J* = 7.3 Hz, 2H), 1.92 – 1.84 (m, 1H), 1.68 – 1.48 (m, 6H), 1.17 (s, 9H), 1.14 – 1.00 (m, 2H), 0.89 – 0.80 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.9, 142.9, 132.2, 131.3, 128.8, 128.7, 128.6, 125.0, 59.6, 56.4, 44.7, 38.7, 30.3, 29.0, 26.0, 25.4;

HRMS calculated for $C_{20}H_{29}N_4O_2S$ $(M+H)^+$ 389.2011, found 389.2018.

(±)-1-Benzyl-5-(*tert*-butyl)-9-fluoro-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.25)



Yield 99%;

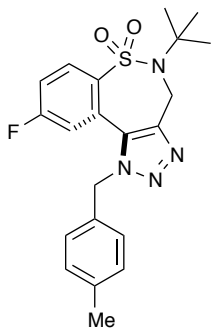
FTIR (neat): 2980, 1585, 1344, 1163 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, J = 8.8 Hz, $^{4}J_{H-F}$ = 5.8 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.24 (d, J = 7.0 Hz, 2H), 7.20 (dd, J = 2.4 Hz, $^{3}J_{H-F}$ = 9.4 Hz, 1H), 7.13 (ddd, J = 9.8, 2.5 Hz, $^{3}J_{H-F}$ = 7.4 Hz, 1H), 5.72 (s, 2H), 5.02 (s, 2H), 1.19 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 164.0 (d, $^{1}J_{C-F}$ = 255.3 Hz), 144.9, 139.0 (d, $^{4}J_{C-F}$ = 3.8 Hz), 134.7, 131.2 (d, $^{3}J_{C-F}$ = 10.1 Hz), 130.4, 129.3, 128.6, 126.7 (d, $^{3}J_{C-F}$ = 8.8 Hz), 126.6, 116.5 (d, $^{2}J_{C-F}$ = 25.2 Hz), 115.2 (d, $^{2}J_{C-F}$ = 21.4 Hz), 59.7, 53.7, 44.7, 29.0;

HRMS calculated for $C_{20}H_{22}FN_4O_2S$ $(M+H)^+$ 401.1447, found 401.1456.

(±)-5-(*tert*-Butyl)-9-fluoro-1-(4-methylbenzyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.26)



Yield 83%;

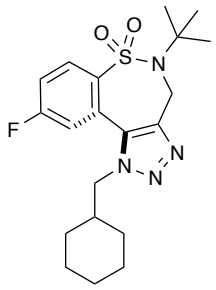
FTIR (neat): 2980, 1585, 1344, 1190, 1163 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, J = 8.7 Hz, $^4J_{H\text{-}F}$ = 5.6 Hz, 1H), 7.24 (dd, J = 2.5 Hz, $^3J_{H\text{-}F}$ = 9.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.12 (ddd, J = 9.0, 2.5 Hz, $^3J_{H\text{-}F}$ = 7.3 Hz, 1H), 5.67 (s, 2H), 5.01 (s, 2H), 2.35 (s, 3H), 1.18 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 164.0 (d, $^1J_{C\text{-}F}$ = 254.0 Hz), 144.8, 138.9 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 138.4, 131.7, 131.2 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 130.3, 129.9, 126.8 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 126.6, 116.6 (d, $^2J_{C\text{-}F}$ = 26.4 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 59.7, 53.5, 44.6, 29.0, 21.1;

HRMS calculated for $C_{21}H_{24}FN_4O_2S$ $(M+H)^+$ 415.1604, found 415.1601.

(±)-5-(*tert*-Butyl)-1-(cyclohexylmethyl)-9-fluoro-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.27)



Yield 63%;

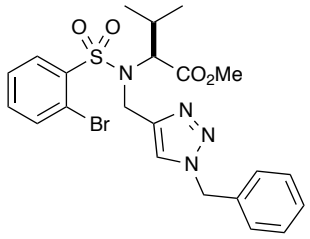
FTIR (neat): 2928, 1583, 1344, 1190, 1163 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 (dd, J = 8.7 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.31 (dd, J = 2.5 Hz, $^3J_{H-F}$ = 9.5 Hz, 1H), 7.22 (ddd, J = 2.5, 8.8 Hz, $^3J_{H-F}$ = 7.6 Hz, 1H), 4.96 (s, 2H), 4.39 (d, J = 7.2 Hz, 2H), 1.89 (dddt, J = 3.6, 7.1, 10.8, 14.5 Hz, 1H), 1.68 – 1.53 (m, 6H), 1.19 (s, 9H), 1.14 – 1.08 (m, 2H), 0.92 – 0.88 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 164.1 (d, $^1J_{C-F}$ = 254.0 Hz), 144.4, 139.1 (d, $^4J_{C-F}$ = 2.5 Hz), 131.4 (d, $^3J_{C-F}$ = 8.8 Hz), 130.3, 127.5 (d, $^3J_{C-F}$ = 8.8 Hz), 116.0 (d, $^2J_{C-F}$ = 25.2 Hz), 115.2 (d, $^2J_{C-F}$ = 21.4 Hz), 59.8, 56.5, 44.7, 38.8, 30.3, 29.0, 25.9, 25.4;

HRMS calculated for $C_{20}H_{28}FN_4O_2S$ $(M+H)^+$ 407.1917, found 407.1933.

(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.28)



Yield 84%;

$[\alpha]_D^{25}$ = +13.43 (*c* = 1.40, CH_2Cl_2);

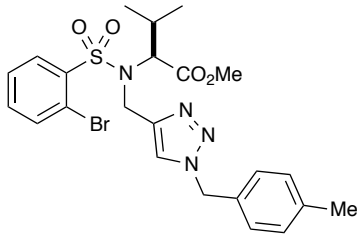
FTIR (neat): 2970, 1338, 1259 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.72 (s, 1H), 7.67 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.44 – 7.32 (m, 5H), 7.25 (dd, *J* = 7.2, 2.0 Hz, 2H), 5.52 (d, *J* = 14.9 Hz, 1H), 5.45 (d, *J* = 14.9 Hz, 1H), 5.08 (s, 2H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.44 (s, 3H), 2.40 (dqq, *J* = 10.5, 6.5, 6.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.5, 145.9, 139.0, 135.3, 134.7, 133.6, 132.8, 129.0, 128.7, 127.9, 127.6, 124.1, 120.1, 66.0, 54.1, 51.6, 41.2, 28.5, 19.6, 19.1;

HRMS calculated for $C_{22}H_{26}BrN_4O_4S$ $(M+H)^+$ 521.0858, found 521.0887.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.29)



Yield 99%;

$[\alpha]_D^{25}$ = +5.65 (*c* = 1.70, CH_2Cl_2);

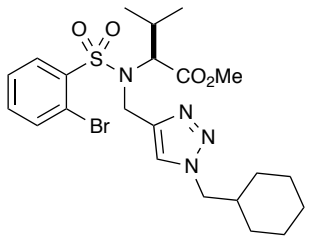
FTIR (neat): 2964, 1734, 1338, 1149 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.70 (s, 1H), 7.68 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.42 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.35 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.48 (d, *J* = 14.8 Hz, 1H), 5.40 (d, *J* = 14.8 Hz, 1H), 5.07 (s, 2H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.44 (s, 3H), 2.40 (dqq, *J* = 10.5, 6.5, 6.5 Hz, 1H), 2.36 (s, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.5, 145.8, 139.0, 138.6, 135.3, 133.6, 132.8, 131.7, 129.7, 127.9, 127.6, 124.0, 120.1, 66.0, 53.9, 51.6, 41.2, 28.5, 21.2, 19.6, 19.1;

HRMS calculated for $C_{23}H_{28}BrN_4O_4S$ $(M+H)^+$ 535.1015, found 535.0983.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.30)



Yield 72%;

$[\alpha]_D^{25}$ = +10.54 (*c* = 1.47, CH_2Cl_2);

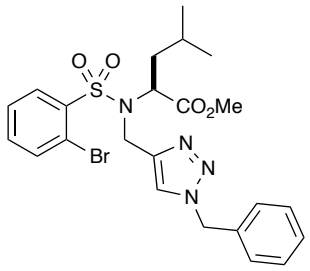
FTIR (neat): 2925, 1338, 1149 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.75 (s, 1H), 7.72 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (td, *J* = 7.8, 1.8 Hz, 1H), 5.13 (d, *J* = 16.7 Hz, 1H), 5.08 (d, *J* = 16.6 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.47 (s, 3H), 2.41 (dqq, *J* = 10.6, 6.6, 6.6 Hz, 1H), 1.87 (m, 1H), 1.78 – 1.55 (m, 4H), 1.31 – 1.12 (m, 4H), 1.07 – 0.93 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.5, 145.4, 139.1, 135.3, 133.6, 132.8, 127.6, 124.6, 120.1, 66.1, 56.5, 51.6, 41.4, 38.8, 30.5, 30.4, 28.5, 26.1, 25.5, 19.6, 19.1;

HRMS calculated for $C_{22}H_{32}BrN_4O_4S$ $(M+H)^+$ 527.1328, found 527.1295.

(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromophenylsulfonamido)-4-methylpentanoate (4.31)



Yield 85%;

$[\alpha]_D^{25}$ = –40.52 (*c* = 2.50, CH_2Cl_2);

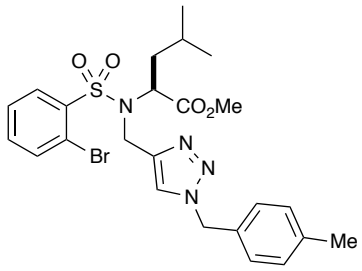
FTIR (neat): 2954, 1740, 1342, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.78 (s, 1H), 7.73 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.46 – 7.36 (m, 5H), 7.31 – 7.28 (m, 2H), 5.51 (s, 2H), 4.93 (d, *J* = 16.9 Hz, 1H), 4.72 (d, *J* = 16.9 Hz, 1H), 4.63 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.50 (s, 3H), 1.84 (ddd, *J* = 15.5, 11.6, 5.2 Hz, 1H), 1.59 (ddd, *J* = 14.3, 9.5, 4.6 Hz, 1H), 1.30 – 1.23 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.58 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.5, 146.1, 139.0, 135.6, 134.7, 133.6, 132.3, 129.1, 128.7, 128.0, 127.6, 124.0, 120.2, 58.9, 54.2, 52.1, 41.7, 38.9, 24.3, 22.4, 21.1;

HRMS calculated for $C_{23}H_{28}BrN_4O_4S$ $(M+H)^+$ 535.1015, found 535.1026.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.32)



Yield 85%;

$[\alpha]_D^{25} = -39.16$ (c = 1.54, CH_2Cl_2);

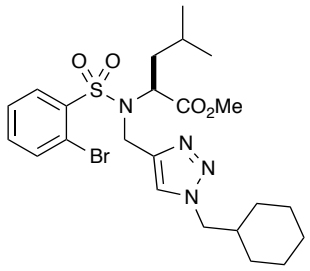
FTIR (neat): 2954, 1742, 1344, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (dd, J = 7.8, 1.8 Hz, 1H), 7.74 (s, 1H), 7.71 (dd, J = 7.8, 1.4 Hz, 1H), 7.42 (td, J = 7.5, 1.4 Hz, 1H), 7.36 (td, J = 7.7, 1.9 Hz, 1H), 7.17 (s, 4H), 5.45 (s, 2H), 4.90 (d, J = 16.9 Hz, 1H), 4.69 (d, J = 16.9 Hz, 1H), 4.61 (dd, J = 10.4, 4.6 Hz, 1H), 3.48 (s, 3H), 2.36 (s, 3H), 1.83 (ddd, J = 14.4, 10.4, 4.1 Hz, 1H), 1.58 (ddd, J = 14.3, 9.6, 4.7 Hz, 1H), 1.30 – 1.20 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.57 (d, J = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 145.9, 139.0, 138.6, 135.6, 133.5, 132.2, 131.7, 129.7, 128.0, 127.5, 123.9, 120.2, 58.9, 54.0, 52.1, 41.7, 38.9, 24.2, 22.4, 21.1;

HRMS calculated for $C_{24}H_{30}BrN_4O_4S$ $(M+H)^+$ 549.1171, found 549.1188.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.33)



Yield 69%;

$[\alpha]_D^{25}$ = +4.69 (*c* = 2.45, CH_2Cl_2);

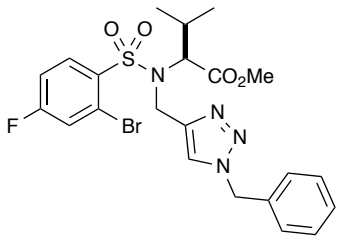
FTIR (neat): 2927, 1742, 1448, 1340, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.80 (s, 1H), 7.76 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.48 (tt, *J* = 7.6, 1.5 Hz, 1H), 7.41 (tt, *J* = 7.6, 1.7 Hz, 1H), 4.96 (d, *J* = 16.6 Hz, 1H), 4.74 (d, *J* = 16.9 Hz, 1H), 4.65 (dd, *J* = 10.4, 4.5 Hz, 1H), 4.19 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.15 (dd, *J* = 13.6, 7.2 Hz, 1H), 3.53 (d, *J* = 2.0 Hz, 3H), 1.88 (ddd, *J* = 14.2, 10.3, 4.1 Hz, 2H), 1.77 – 1.57 (m, 6H), 1.30 – 1.16 (m, 4H), 1.06 – 0.97 (m, 2H), 0.89 (dd, *J* = 6.5, 1.1 Hz, 3H), 0.64 (dd, *J* = 6.6, 2.9 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 145.5, 139.0, 135.6, 133.6, 132.3, 127.6, 124.6, 120.2, 59.0, 56.6, 52.1, 41.8, 38.9, 38.8, 30.9, 30.5, 26.0, 25.5, 25.5, 24.3, 22.5, 21.1;

HRMS calculated for $C_{23}H_{34}BrN_4O_4S$ $(M+H)^+$ 541.1484, found 541.1498.

(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-4-fluorophenylsulfonamido)-3-methylbutanoate (4.34)



Yield 99%;

$[\alpha]_D^{25}$ = +13.19 (*c* = 1.35, CH_2Cl_2);

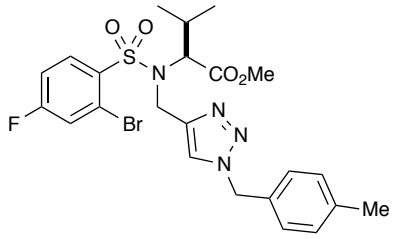
FTIR (neat): 2964, 1733, 1581, 1339, 1161 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.72 (s, 1H), 7.43 – 7.35 (m, 4H), 7.25 (m, 2H), 7.11 (ddd, *J* = 9.5, 2.5 Hz, $^3J_{H-F}$ = 7.5 Hz, 1H), 5.54 (d, *J* = 14.8 Hz, 1H), 5.47 (d, *J* = 14.8 Hz, 1H), 5.06 (s, 2H), 3.87 (d, *J* = 10.5 Hz, 1H), 3.51 (s, 3H), 2.41 (dqq, *J* = 10.6, 6.6, 6.4 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.6, 164.1 (d, $^1J_{C-F}$ = 259.1 Hz), 145.6, 135.4 (d, $^4J_{C-F}$ = 3.8 Hz), 134.9 (d, $^3J_{C-F}$ = 10.1 Hz), 134.7, 129.1, 128.7, 127.9, 124.0, 122.6 (d, $^2J_{C-F}$ = 23.9 Hz), 121.4, (d, $^3J_{C-F}$ = 10.1 Hz), 114.7 (d, $^2J_{C-F}$ = 21.4 Hz), 66.1, 54.1, 51.7, 41.1, 28.5, 19.6, 19.1;

HRMS calculated for $C_{22}H_{25}BrFN_4O_4S$ $(M+H)^+$ 539.0764, found 539.0731.

(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.35)



Yield 77%;

$[\alpha]_D^{25}$ = +12.90 (*c* = 1.55, CH_2Cl_2);

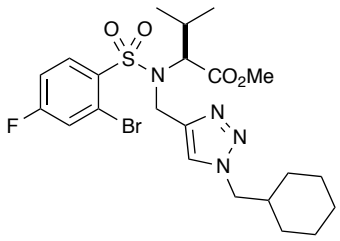
FTIR (neat): 2965, 1741, 1586, 1338, 1150 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (dd, *J* = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.67 (s, 1H), 7.38 (dd, *J* = 2.6 Hz, $^3J_{H-F}$ = 7.9 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.09 (ddd, *J* = 9.0, 2.6 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 5.47 (d, *J* = 14.7 Hz, 1H), 5.40 (d, *J* = 14.8 Hz, 1H), 5.03 (s, 2H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.50 (s, 3H), 2.39 (dqq, *J* = 10.5, 6.6, 6.6 Hz, 1H), 2.35 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.6, 164.1 (d, $^1J_{C-F}$ = 259.1 Hz), 145.5, 138.6, 135.4 (d, $^4J_{C-F}$ = 3.8 Hz), 134.9 (d, $^3J_{C-F}$ = 10.1 Hz), 131.6, 129.7, 127.9, 123.9, 122.6 (d, $^2J_{C-F}$ = 25.2 Hz), 121.4 (d, $^3J_{C-F}$ = 11.3 Hz), 114.7 (d, $^2J_{C-F}$ = 21.4 Hz), 66.1, 53.9, 51.7, 41.1, 28.5, 21.2, 19.6, 19.1;

HRMS calculated for $C_{23}H_{27}BrFN_4O_4S$ $(M+H)^+$ 553.0920, found 553.0937.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.36)



Yield 70%;

$[\alpha]_D^{25}$ = +7.13 (*c* = 1.94, CH_2Cl_2);

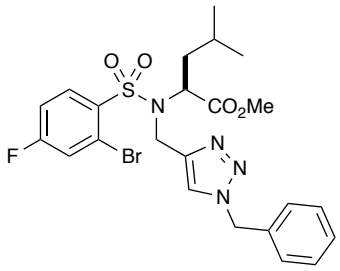
FTIR (neat): 2965, 1741, 1586, 1338, 1150 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, *J* = 9.0 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.73 (s, 1H), 7.45 (dd, *J* = 2.4 Hz, $^3J_{H-F}$ = 7.8 Hz, 1H), 7.14 (ddd, *J* = 9.4, 2.4 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 5.10 (d, *J* = 16.7 Hz, 1H), 5.05 (d, *J* = 16.7 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 2H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.52 (s, 3H), 2.41 (dqq, *J* = 10.6, 6.6, 6.5 Hz, 1H), 1.86 (dtd, *J* = 14.9, 7.3, 3.7 Hz, 1H), 1.75 – 1.58 (m, 5H), 1.30 – 1.13 (m, 3H), 1.05 – 0.92 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.5, 164.1 (d, $^1J_{C-F}$ = 259.1 Hz), 145.1, 135.5 (d, $^4J_{C-F}$ = 3.8 Hz), 135.0 (d, $^3J_{C-F}$ = 8.8 Hz), 124.5, 122.6 (d, $^2J_{C-F}$ = 25.2 Hz), 121.5 (d, $^3J_{C-F}$ = 10.1 Hz), 114.7 (d, $^2J_{C-F}$ = 21.4 Hz), 66.2, 56.5, 51.7, 41.3, 38.8, 30.5, 30.4, 28.5, 26.1, 25.5, 19.6, 19.1;

HRMS calculated for $C_{22}H_{31}BrFN_4O_4S$ $(M+H)^+$ 545.1233, found 545.1218.

(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-4-fluorophenylsulfonamido)-4-methylpentanoate (4.37)



Yield 94%;

$[\alpha]_D^{25} = -32.44$ ($c = 0.78$, CH_2Cl_2);

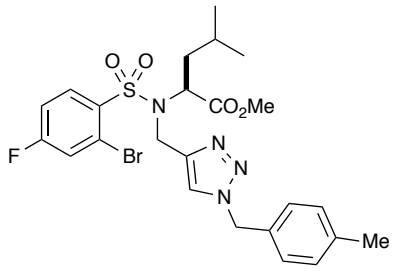
FTIR (neat): 2954, 1740, 1581, 1342, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, J = 8.9 Hz, $^4J_{H\text{-}F}$ = 5.8 Hz, 1H), 7.76 (s, 1H), 7.44 (dd, J = 2.5 Hz, $^3J_{H\text{-}F}$ = 8.0 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.30 – 7.28 (m, 2H), 7.11 (ddd, J = 9.8, 2.5 Hz, $^3J_{H\text{-}F}$ = 7.4 Hz, 1H), 5.50 (s, 2H), 4.87 (d, J = 16.9 Hz, 1H), 4.68 (d, J = 16.9 Hz, 1H), 4.61 (dd, J = 10.4, 4.6 Hz, 1H), 3.54 (s, 3H), 1.83 (ddd, J = 14.4, 10.4, 4.0 Hz, 1H), 1.59 (ddd, J = 14.3, 9.5, 4.7 Hz, 1H), 1.29 – 1.17 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.58 (d, J = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 164.0 (d, $^1J_{C\text{-}F}$ = 259.1 Hz), 145.8, 135.4 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 134.7, 134.2 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 129.1, 128.7, 128.0, 124.0, 123.0 (d, $^2J_{C\text{-}F}$ = 25.2 Hz), 121.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 114.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 59.0, 54.2, 52.2, 41.6, 38.9, 24.3, 22.4, 21.1;

HRMS calculated for $C_{23}H_{27}BrFN_4O_4S$ $(M+H)^+$ 553.0920, found 553.0928.

(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.38)



Yield 97%;

$[\alpha]_D^{25}$ = –40.29 (*c* = 1.72, CH_2Cl_2);

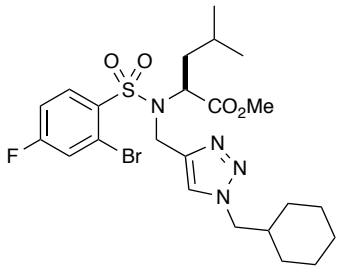
FTIR (neat): 2955, 1742, 1582, 1344, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.73 (s, 1H), 7.44 (dd, *J* = 2.6 Hz, $^3J_{H-F}$ = 8.0 Hz, 1H), 7.18 (s, 4H), 7.12 (ddd, *J* = 9.9, 2.6 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 5.45 (s, 2H), 4.86 (d, *J* = 16.9 Hz, 1H), 4.67 (d, *J* = 16.9 Hz, 1H), 4.61 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.54 (s, 3H), 2.36 (s, 3H), 1.84 (ddd, *J* = 14.4, 10.4, 4.1 Hz, 1H), 1.59 (ddd, *J* = 14.2, 9.6, 4.7 Hz, 1H), 1.28 – 1.22 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.59 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.5, 164.0 (d, $^1J_{C-F}$ = 259.1 Hz), 145.7, 138.7, 135.4 (d, $^4J_{C-F}$ = 2.5 Hz), 134.2 (d, $^3J_{C-F}$ = 10.1 Hz), 131.6, 129.7, 128.0, 123.9, 122.9 (d, $^2J_{C-F}$ = 25.2 Hz), 121.5 (d, $^3J_{C-F}$ = 10.1 Hz), 114.7 (d, $^2J_{C-F}$ = 25.2 Hz), 59.0, 54.0, 52.2, 41.6, 38.9, 24.3, 22.4, 21.1, 21.0;

HRMS calculated for $C_{24}H_{29}BrFN_4O_4S$ $(M+H)^+$ 567.1077, found 567.1072.

(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorophenylsulfonamido)-4-methylpentanoate (4.39)



Yield 98%;

$[\alpha]_D^{25} = -36.96$ ($c = 0.63$, CH_2Cl_2);

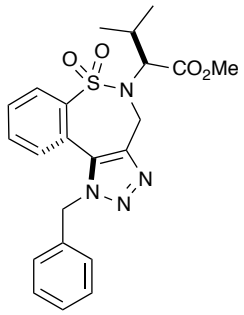
FTIR (neat): 2928, 2853, 1742, 1582, 1344, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.78 (s, 1H), 7.48 (dd, J = 2.5 Hz, $^3J_{H-F}$ = 8.0 Hz, 1H), 7.15 (ddd, J = 9.0, 2.5 Hz, $^3J_{H-F}$ = 7.5 Hz 1H), 4.91 (d, J = 16.9 Hz, 1H), 4.70 (d, J = 16.9 Hz, 1H), 4.63 (dd, J = 10.4, 4.5 Hz, 1H), 4.18 (dd, J = 13.5, 7.2 Hz, 1H), 4.13 (dd, J = 13.7, 7.3 Hz, 1H), 3.57 (s, 3H), 1.91 – 1.84 (m, 2H), 1.77 – 1.68 (m, 3H), 1.63 – 1.58 (m, 3H), 1.33 – 1.14 (m, 4H), 1.05 – 0.96 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H), 0.64 (d, J = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 164.0 (d, $^1J_{C-F}$ = 259.1 Hz), 145.2, 135.4 (d, $^4J_{C-F}$ = 3.8 Hz), 134.2 (d, $^3J_{C-F}$ = 10.1 Hz), 124.5, 122.5 (d, $^2J_{C-F}$ = 23.9 Hz), 121.6 (d, $^3J_{C-F}$ = 10.1 Hz), 114.7 (d, $^2J_{C-F}$ = 21.3 Hz), 59.1, 56.6, 52.2, 41.8, 38.9, 38.8, 30.5, 26.0, 25.5, 25.4, 24.3, 22.5, 21.1;

HRMS calculated for $C_{23}H_{33}BrFN_4O_4S$ $(M+H)^+$ 559.1390, found 559.1396.

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.40)



Yield 67%;

Mp 83 ºC;

$[\alpha]_D^{25}$ = +14.10 (*c* = 3.00, CH_2Cl_2);

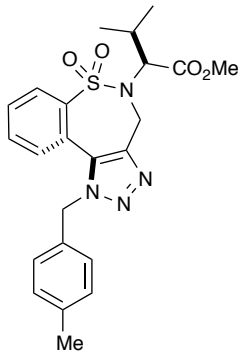
FTIR (neat): 2966, 2933, 1737, 1346, 1157 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.96 (d, *J* = 16.2 Hz, 1H), 5.81 (d, *J* = 16.2 Hz, 1H), 5.05 (d, *J* = 16.2 Hz, 1H), 4.91 (d, *J* = 16.2 Hz, 1H), 3.82 (d, *J* = 10.5 Hz, 1H), 3.10 (s, 3H), 2.16 (dqq, *J* = 9.2, 6.5, 6.2 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.3, 142.9, 140.6, 135.2, 132.3, 131.0, 129.1, 128.9, 128.8, 128.5, 128.3, 126.4, 124.2, 65.3, 52.9, 51.7, 43.1, 28.9, 19.3, 19.1;

HRMS calculated for $C_{22}H_{25}N_4O_4S$ $(M+H)^+$ 441.1597, found 441.1585.

(*S*)-Methyl 3-methyl-2-((*S*$_a$)-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)butanoate (4.41)



Yield 54%;

$[\alpha]_D^{25}$ = +0.17 (*c* = 1.15, CH_2Cl_2);

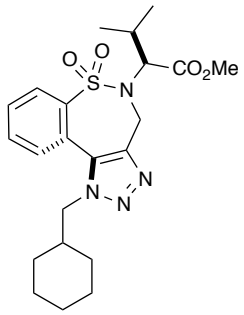
FTIR (neat): 2964, 2927, 1348, 1157 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (d, *J* = 7.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.40 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 5.78 (d, *J* = 16.1 Hz, 1H), 5.48 (d, *J* = 16.0 Hz, 1H), 5.06 (d, *J* = 16.3 Hz, 1H), 5.01(d, *J* = 16.4 Hz, 1H), 3.92 (d, *J* = 10.6 Hz, 1H), 3.10 (s, 3H), 2.34 (s, 3H), 2.17 (dqq, *J* = 10.6, 6.4, 6.4 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.3, 142.8, 140.6, 138.1, 132.3, 132.2, 131.0, 129.8, 129.0, 128.8, 128.5, 126.4, 124.3, 65.3, 52.8, 51.7, 43.1, 28.9, 21.1, 19.3, 19.1;

HRMS calculated for $C_{23}H_{27}N_4O_4S$ $(M+H)^+$ 455.1753, found 455.1748.

(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.42)



Yield 66%;

$[\alpha]_D^{25}$ = +0.50 (*c* = 2.02, CH_2Cl_2);

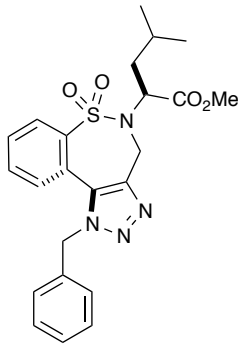
FTIR (neat): 2930, 1446, 1348, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.68 (td, *J* = 7.7, 1.3 Hz, 1H), 7.55 – 7.50 (m, 2H), 5.02 (d, *J* = 16.1 Hz, 1H), 4.94 (d, *J* = 16.1 Hz, 1H), 4.41 (dd, *J* = 13.7, 6.9 Hz, 1H), 4.29 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.94 (d, *J* = 10.5 Hz, 1H), 3.16 (s, 3H), 2.15 (dqq, *J* = 10.5, 6.8, 6.6 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.68 – 1.51 (m, 5H), 1.18 – 1.06 (m, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.95 – 0.85 (m, 1H), 0.79 – 0.71 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.4, 142.4, 140.8, 132.4, 131.0, 128.8, 128.7, 128.4, 124.9, 65.3, 55.8, 51.7, 43.1, 38.7, 30.3, 30.2, 28.9, 26.0, 25.4, 25.3, 19.3, 19.1;

HRMS calculated for $C_{22}H_{31}N_4O_4S$ $(M+H)^+$ 447.2066, found 447.2034.

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.43)



Yield 60%;

Mp 145 ºC;

$[\alpha]_D^{25}$ = +1.08 (*c* = 2.69, CH_2Cl_2);

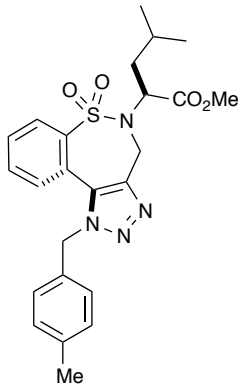
FTIR (neat): 2933, 1521, 1319, 1134 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.43 – 7.33 (m, 4H), 7.21 (d, *J* = 7.1 Hz, 2H), 5.82 (d, *J* = 16.2 Hz, 1H), 5.60 (d, *J* = 16.0 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.83 (d, *J* = 15.7 Hz, 1H), 4.57 (dd, *J* = 5.4, 1.0 Hz, 1H), 3.32 (s, 3H), 1.74 – 1.65 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.2, 142.6, 141.0, 135.2, 132.3, 131.7, 129.1, 128.9, 128.6, 128.3, 128.2, 126.5, 124.5, 58.2, 52.9, 52.1, 43.1, 38.6, 24.5, 23.0, 21.0;

HRMS calculated for $C_{23}H_{27}N_4O_4S$ $(M+H)^+$ 455.1753, found 455.1750.

(*S*)-Methyl 4-methyl-2-((*S*$_a$)-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)pentanoate (4.44)



Yield 33%;

$[\alpha]_D^{25}$ = +0.80 (*c* = 0.50, CH_2Cl_2);

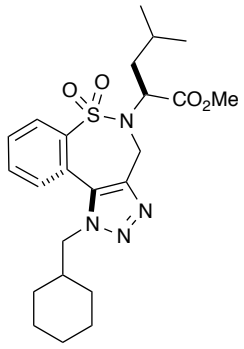
FTIR (neat): 2955, 1742, 1346, 1254, 1161 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.52 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.42 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.53 (d, *J* = 16.0 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H), 4.56 (dd, *J* = 9.1, 5.4 Hz, 1H), 3.30 (s, 3H), 2.34 (s, 3H), 1.70 – 1.63 (m, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.1, 142.5, 141.0, 138.1, 132.3, 132.2, 129.8, 129.3, 129.0, 128.5, 128.2, 126.5, 124.5, 58.2, 52.7, 52.1, 43.1, 38.6, 24.5, 23.0, 21.1, 21.0;

HRMS calculated for $C_{24}H_{28}N_4O_4SNa$ $(M+Na)^+$ 491.1729, found 491.1743.

(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.45)



Yield 48%;

$[\alpha]_D^{25}$ = –0.22 (*c* = 1.35, CH_2Cl_2);

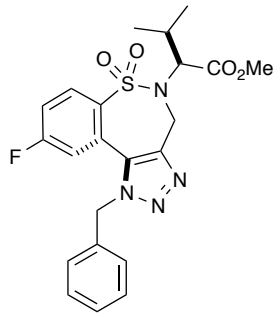
FTIR (neat): 2925, 1742, 1346, 1159 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.68 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.51 (dt, *J* = 7.7, 1.2 Hz, 1H), 4.84 (d, *J* = 15.4 Hz, 1H), 4.74 (d, *J* = 15.3 Hz, 1H), 4.58 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.40 (dd, *J* = 13.7, 7.1 Hz, 1H), 4.32 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.34 (s, 3H), 1.92 – 1.82 (m, 1H), 1.72 – 1.53 (m, 8H), 1.17 – 1.06 (m, 3H), 0.94 (d, *J* = 5.8 Hz, 3H), 0.92 (d, *J* = 5.8 Hz, 3H), 0.89 – 0.77 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.2, 142.1, 141.2, 132.4, 131.7, 128.6, 128.4, 128.2, 125.1, 58.3, 55.7, 52.1, 43.0, 38.7, 38.5, 30.3, 30.2, 26.0, 25.4, 25.4, 24.5, 23.0, 21.0;

HRMS calculated for $C_{23}H_{33}N_4O_4S$ $(M+H)^+$ 461.2223, found 461.2203.

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.46)



Yield 34%;

$[\alpha]_D^{25}$ = –0.92 (*c* = 1.52, CH_2Cl_2);

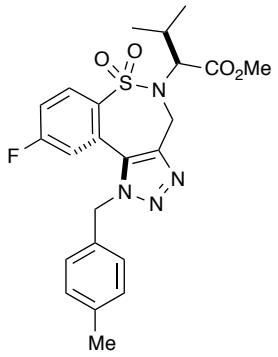
FTIR (neat): 2966, 1738, 1585, 1350, 1155 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (dd, *J* = 9.4 Hz, $^4J_{H\text{-}F}$ = 5.7 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.18 (d, *J* = 7.0 Hz, 2H) 7.13 – 7.10 (m, 2H), 5.84 (d, *J* = 16.2 Hz, 1H), 5.55 (d, *J* = 16.2 Hz, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 5.02 (d, *J* = 16.5 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 3.17 (s, 3H), 2.24 – 2.08 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.3, 164.2 (d, $^1J_{C\text{-}F}$ = 255.3 Hz), 143.4, 136.7 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 134.7, 131.5 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 130.0, 129.3, 128.5, 126.9 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 126.5, 116.4 (d, $^2J_{C\text{-}F}$ = 26.4 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 65.3, 53.2, 51.7, 43.2, 29.0, 19.3, 19.1;

HRMS calculated for $C_{22}H_{24}FN_4O_4S$ $(M+H)^+$ 459.1502, found 459.1455.

(*S*)-Methyl 2-((*S*$_a$)-9-fluoro-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.47)



Yield 31%;

$[\alpha]_D^{25}$ = –0.61 (*c* = 1.33, CH_2Cl_2);

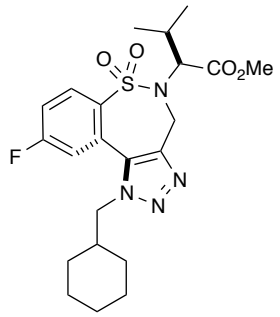
FTIR (neat): 2972, 1737, 1585, 1350, 1155 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (dd, *J* = 8.6 Hz, $^4J_{H\text{-}F}$ = 5.7 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.15 – 7.12 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.80 (d, *J* = 16.0 Hz, 1H), 5.49 (d, *J* = 16.1 Hz, 1H), 5.06 (d, *J* = 16.3 Hz, 1H), 5.01 (d, *J* = 18.1 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 3.17 (s, 3H), 2.35 (s, 3H), 2.18 (dqq, *J* = 10.5, 6.4, 6.3 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.3, 164.2 (d, $^1J_{C\text{-}F}$ = 255.3 Hz), 143.3, 138.4, 136.7 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 131.7, 131.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 129.9, 128.5, 126.9 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 126.5, 116.5 (d, $^2J_{C\text{-}F}$ = 25.2 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 65.3, 53.1, 51.7, 43.2, 29.0, 21.1, 19.3, 19.1;

HRMS calculated for $C_{23}H_{26}FN_4O_4S$ $(M+H)^+$ 473.1659, found 473.1629.

(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.48)



Yield 36%;

$[\alpha]_D^{25}$ = –0.34 (*c* = 1.18, CH_2Cl_2);

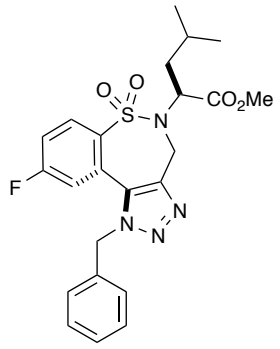
FTIR (neat): 2927, 1737, 1585, 1350, 1155 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (dd, *J* = 8.8 Hz, $^4J_{H\text{-}F}$ = 5.7 Hz, 1H), 7.24 (dd, *J* = 2.5 Hz, $^3J_{H\text{-}F}$ = 9.2 Hz, 1H), 7.19 (ddd, *J* = 8.6, 2.5 Hz, $^3J_{H\text{-}F}$ = 7.8 Hz, 1H), 5.02 (d, *J* = 16.3 Hz, 1H), 4.94 (d, *J* = 16.3 Hz, 1H), 4.42 (dd, *J* = 13.8, 6.9 Hz, 1H), 4.26 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.93 (d, *J* = 10.4 Hz, 1H), 3.25 (s, 3H), 2.26 (dqq, *J* = 10.2, 6.6, 6.6 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.70 – 1.51 (m, 4H), 1.22 – 1.09 (m, 4H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 – 0.71 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.4, 164.3 (d, $^1J_{C\text{-}F}$ = 255.3 Hz), 142.8, 137.0, (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 131.6 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 130.1, 127.8 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 116.1 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 65.3, 55.9, 51.8, 43.2, 38.8, 30.3, 30.2, 29.0, 26.0, 25.4, 25.3, 19.4, 19.1;

HRMS calculated for $C_{22}H_{30}FN_4O_4S$ $(M+H)^+$ 465.1972, found 465.1994.

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.49)



Yield 25%;

$[\alpha]_D^{25} = -1.09$ (c = 1.56, CH_2Cl_2);

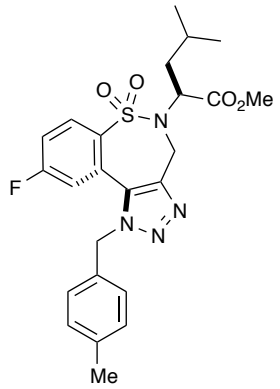
FTIR (neat): 2956, 1742, 1587, 1348, 1159 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (dd, J = 8.7 Hz, $^4J_{H-F}$ = 5.6 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.20 (d, J = 7.2 Hz, 2H), 7.14 – 7.08 (m, 2H), 5.82 (d, J = 16.1 Hz, 1H), 5.59 (d, J = 16.1 Hz, 1H), 4.92 (d, J = 5.8 Hz, 1H), 4.80 (d, J = 5.8 Hz, 1H), 4.55 (dd, J = 8.8, 5.0 Hz, 1H), 3.35 (s, 3H), 1.74 – 1.65 (m, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.1, 164.2 (d, $^1J_{C-F}$ = 255.3 Hz), 143.1, 137.1, (d, $^4J_{C-F}$ = 3.8 Hz), 134.7, 130.8 (d, $^3J_{C-F}$ = 8.8 Hz), 130.7, 129.3, 128.5, 127.1 (d, $^3J_{C-F}$ = 8.8 Hz), 126.6, 116.4 (d, $^2J_{C-F}$ = 26.4 Hz), 114.9 (d, $^2J_{C-F}$ = 21.4 Hz), 58.3, 53.2, 52.2, 43.1, 38.7, 24.6, 23.0, 20.9;

HRMS calculated for $C_{23}H_{26}FN_4O_4S$ $(M+H)^+$ 473.1659, found 473.1646.

(*S*)-Methyl 2-((*S*$_a$)-9-fluoro-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.50)



Yield 86%;

$[\alpha]_D^{25}$ = +21.92 (*c* = 2.29, CH_2Cl_2);

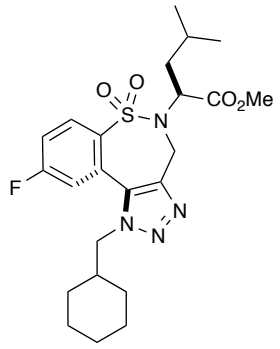
FTIR (neat): 2954, 1741, 1348, 1159 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (dd, *J* = 8.7 Hz, $^4J_{H\text{-}F}$ = 5.6 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.15 (dd, *J* = 2.5 Hz, $^3J_{H\text{-}F}$ = 9.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.09 (m, 1H), 5.78 (d, *J* = 16.0 Hz, 1H), 5.53 (d, *J* = 16.0 Hz, 1H), 4.92 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.55 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.35 (s, 3H), 2.35 (s, 3H), 1.74 – 1.65 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.1, 164.2 (d, $^1J_{C\text{-}F}$ = 255.3 Hz), 143.1, 138.4, 137.0 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 131.7, 130.7 (d, $^3J_{C\text{-}F}$ = 8.8Hz), 130.6, 129.9, 127.2 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 126.6, 116.5 (d, $^2J_{C\text{-}F}$ = 25.2 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 58.3, 53.0, 52.2, 43.1, 38.7, 24.6, 23.0, 21.1, 20.9;

HRMS calculated for $C_{24}H_{28}FN_4O_4S$ $(M+H)^+$ 487.1815, found 487.1803.

(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.51)



Yield 51%;

$[\alpha]_D^{25}$ = +10.49 (*c* = 2.14, CH_2Cl_2);

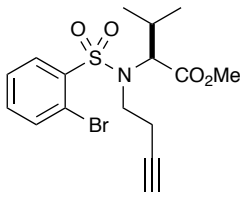
FTIR (neat): 2927, 1742, 1585, 1450, 1348, 1159 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (dd, *J* = 8.8 Hz, $^4J_{H-F}$ = 5.6 Hz, 1H), 7.27 (dd, *J* = 2.4 Hz, $^3J_{H-F}$ = 9.1 Hz, 1H), 7.17 (ddd, *J* = 8.8, 2.5 Hz, $^3J_{H-F}$ = 7.7 Hz, 1H), 4.84 (d, *J* = 15.4 Hz, 1H), 4.73 (d, *J* = 15.5Hz, 1H), 4.58 (dd, *J* = 11.0, 5.9 Hz, 1H), 4.41 (dd, *J* = 13.8, 7.1 Hz, 1H), 4.30 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.40 (s, 3H), 1.92 – 1.84 (m, 1H), 1.74 – 1.61 (m, 7H), 1.19 – 1.08 (m, 4H), 0.96 (d, *J* = 6.1 Hz, 3H), 0.95 (d, *J* = 5.6 Hz, 3H), 0.92 – 0.78 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.2, 164.2 (d, $^1J_{C-F}$ = 255.3 Hz), 142.5, 137.2 (d, $^4J_{C-F}$ = 3.8 Hz), 130.9 (d, $^3J_{C-F}$ = 10.6 Hz), 130.8, 127.8 (d, $^3J_{C-F}$ = 10.1 Hz), 116.0 (d, $^2J_{C-F}$ = 23.9 Hz), 115.0 (d, $^2J_{C-F}$ = 21.4 Hz), 58.3, 55.7, 52.2, 42.9, 38.8, 38.5, 30.3, 30.2, 25.9, 25.4, 25.3, 24.5, 23.1, 20.9;

HRMS calculated for $C_{23}H_{32}FN_4O_4S$ $(M+H)^+$ 479.2128, found 479.2150.

(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)phenylsulfonamido)-3-methylbutanoate (4.52)



Yield 84%;

$[\alpha]_D^{25} = -15.93$ (c = 1.53, CH_2Cl_2);

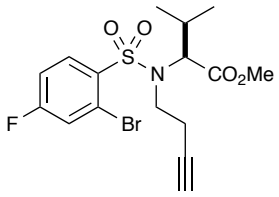
FTIR (neat): 3286, 2966, 1739, 1340, 1151 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J = 7.9, 1.7 Hz, 1H), 7.73 (dd, J = 7.8, 1.3 Hz, 1H), 7.47 (td, J = 7.1, 3.5 Hz, 1H), 7.40 (td, J = 7.6, 1.7 Hz, 1H), 3.90 (d, J = 10.3 Hz, 1H), 3.88 – 3.74 (m, 2H), 3.55 (s, 3H), 2.79 (dddd, J = 16.2, 10.6, 5.5, 2.7 Hz, 1H), 2.49 (dddd, J = 16.4, 10.8, 5.7, 2.6 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.02 (t, J = 2.6 Hz, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.9, 139.0, 135.5, 133.7, 132.8, 127.6, 120.3, 81.0, 70.2, 65.7, 51.7, 44.7, 28.9, 20.8, 19.8, 19.3;

HRMS calculated for $C_{16}H_{21}BrNO_4S$ $(M+H)^+$ 402.0375, found 402.0360.

(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.53)



Yield 91%;

$[\alpha]_D^{25}$ = +39.58 (*c* = 7.87, CH_2Cl_2);

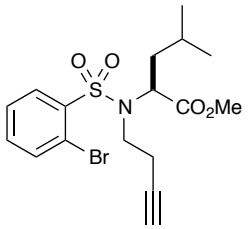
FTIR (neat): 3290, 2968, 1739, 1581, 1465, 1344, 1163 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz,1H), 7.46 (dd, *J* = 2.6 Hz, $^3J_{H-F}$ = 8.0 Hz, 1H), 7.17 (ddd, *J* = 9.9, 2.6 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 3.87 (d, *J* = 10.3 Hz, 1H), 3.90 – 3.72 (m, 2H), 3.57 (s, 3H), 2.78 (dddd, *J* = 16.2, 10.5, 5.6, 2.7 Hz, 1H), 2.48 (dddd, *J* = 16.3, 10.8, 5.7, 2.7 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 170.8, 164.1 (d, $^1J_{C-F}$ = 260.3 Hz), 135.3 (d, $^4J_{C-F}$ = 3.8 Hz), 134.8 (d, $^3J_{C-F}$ = 8.8 Hz), 122.8 (d, $^2J_{C-F}$ = 25.2 Hz), 121.7 (d, $^3J_{C-F}$ = 10.1 Hz), 114.8 (d, $^2J_{C-F}$ = 21.4 Hz), 80.8, 70.3, 65.8, 51.8, 44.8, 28.9, 20.8, 19.8, 19.3;

HRMS calculated for $C_{16}H_{23}BrFN_2O_4S$ $(M+NH_4)^+$ 437.0546, found 437.0559.

(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)phenylsulfonamido)-4-methylpentanoate (4.54)



Yield 52%;

$[\alpha]_D^{25}$ = –45.13 (*c* = 1.54, CH_2Cl_2);

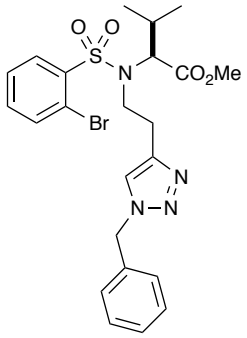
FTIR (neat): 3285, 2955, 1742, 1344, 1155 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.47 (td, *J* = 7.8, 1.3 Hz, 1H), 7.40 (td, *J* = 7.7, 1.8 Hz, 1H), 4.55 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.70 (ddd, *J* = 16.0, 11.1, 5.2 Hz, 1H), 3.57 (s, 3H), 3.51 (ddd, *J* = 16.0, 11.1, 5.2 Hz, 1H), 2.78 (dddd, *J* = 16.3, 11.1, 5.1, 2.7 Hz, 1H), 2.46 (dddd, *J* = 16.4, 11.1, 5.3, 2.7 Hz, 1H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.63 (dd, *J* = 14.9, 6.1 Hz, 1H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 138.8, 135.6, 133.6, 132.6, 127.6, 120.4, 80.9, 70.3, 58.4, 52.2, 45.0, 39.5, 24.5, 22.6, 21.6, 21.0;

HRMS calculated for $C_{17}H_{26}BrN_2O_4S$ $(M+NH_4)^+$ 433.0797, found 433.0781.

(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.55)



Yield 78%;

$[\alpha]_D^{25}$ = –25.45 (*c* = 1.56, CH_2Cl_2);

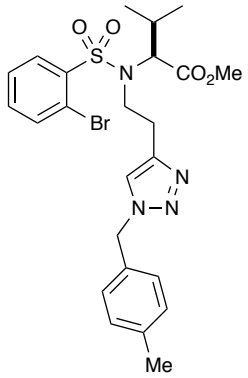
FTIR (neat): 2966, 1733, 1338, 1149 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.45 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.40 – 7.36 (m, 4H), 7.30 – 7.28 (m, 3H), 5.50 (s, 2H), 3.99 (ddd, *J* = 16.6, 11.4, 5.8 Hz, 1H), 3.93 (d, *J* = 9.6 Hz, 1H), 3.86 (ddd, *J* = 16.3, 11.6, 4.9 Hz, 1H), 3.53 (s, 3H), 3.23 (ddd, *J* = 14.1, 11.2, 4.8 Hz, 1H), 3.03 (ddd, *J* = 14.1, 11.7, 5.8 Hz, 1H), 2.22 (dqq, *J* = 16.8, 6.7, 6.7 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.0, 145.2, 139.2, 135.5, 134.7, 133.6, 132.7, 129.1, 128.7, 128.1, 127.6, 121.3, 120.3, 65.9, 54.1, 51.7, 45.7, 28.8, 27.5, 19.9, 19.3;

HRMS calculated for $C_{23}H_{28}BrN_4O_4S$ $(M+H)^+$ 535.1015, found 535.1037.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.56)



Yield 82%;

$[\alpha]_D^{25} = -32.80$ (c = 1.63, CH_2Cl_2);

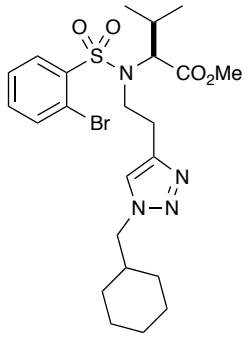
FTIR (neat): 2964, 1740, 1340, 1147 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (dt, J = 7.7, 1.6 Hz, 1H), 7.27 (s, 1H), 7.19 (d, J = 9.7 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 3.97 (ddd, J = 15.3, 11.4, 5.7 Hz, 1H), 3.93 (d, J = 10.6 Hz, 1H), 3.85 (ddd, J = 15.3, 11.5, 4.9 Hz, 1H), 3.52 (s, 3H), 3.22 (ddd, J = 14.2, 11.5, 4.8 Hz, 1H), 3.01 (ddd, J = 14.1, 11.5, 5.7 Hz, 1H), 2.36 (s, 3H), 2.21 (ddq, J = 10.3, 6.6, 6.6 Hz, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.9, 145.1, 139.2, 138.6, 135.5, 133.6, 132.7, 131.7, 129.7, 128.1, 127.6, 121.2, 120.3, 65.8, 53.9, 51.7, 45.7, 28.8, 27.5, 21.2, 19.9, 19.3;

HRMS calculated for $C_{24}H_{30}BrN_4O_4S$ $(M+H)^+$ 549.1171, found 549.1176.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.57)



Yield 81%;

$[\alpha]_D^{25} = -34.13$ (c = 1.42, CH_2Cl_2);

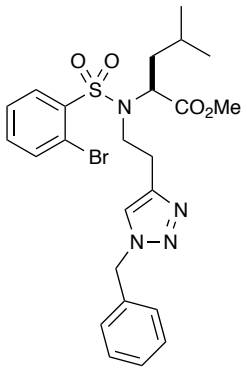
FTIR (neat): 2927, 1740, 1340, 1150 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 7.9, 1.7 Hz, 1H), 7.72 (dd, J = 7.8, 1.2 Hz, 1H), 7.47 (dt, J = 7.6, 1.3 Hz, 1H), 7.39 (dt, J = 7.8, 1.7 Hz, 1H), 7.35 (s, 1H), 4.14 (d, J = 7.2 Hz, 2H), 4.01 (ddd, J = 15.2, 11.2, 5.8 Hz, 1H), 3.94 (d, J = 10.3 Hz, 1H), 3.89 (ddd, J = 15.3, 11.5, 4.9 Hz, 1H), 3.54 (s, 3H), 3.25 (ddd, J = 14.2, 11.3, 4.9 Hz, 1H), 3.06 (ddd, J = 14.1, 11.4, 5.8 Hz, 1H), 2.24 (dqq, J = 10.4, 6.6, 6.6 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.76 – 1.64 (m, 4H), 1.28 – 1.14 (m, 3H), 1.04 (d, J = 6.6 Hz, 3H), 0.99 – 0.97 (m, 3H), 0.92 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.9, 144.5, 139.2, 135.5, 133.6, 132.7, 127.6, 121.8, 120.3, 65.9, 56.4, 51.7, 45.8, 38.8, 30.5, 28.9, 27.5, 26.1, 25.5, 19.9, 19.3;

HRMS calculated for $C_{23}H_{34}BrN_4O_4S$ $(M+H)^+$ 541.1484, found 541.1492.

(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromophenylsulfonamido)-4-methylpentanoate (4.58)



Yield 98%;

$[\alpha]_D^{25} = -50.53$ (*c* = 1.42, CH_2Cl_2);

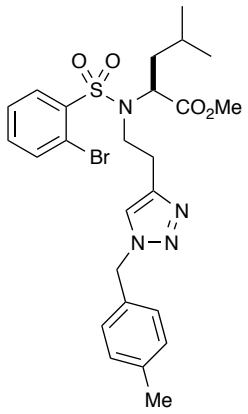
FTIR (neat): 2954, 1742, 1433, 1340, 1153 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.71 (d, *J* = 7.8, 1.3 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.41 – 7.35 (m, 4H), 7.29 – 7.27 (m, 3H), 5.50 (s, 2H), 4.57 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.78 (ddd, *J* = 15.7, 11.2, 5.0 Hz, 1H), 3.66 (ddd, *J* = 15.4, 11.1, 5.8 Hz, 1H), 3.53 (s, 3H), 3.22 (ddd, *J* = 14.3, 11.0, 5.0 Hz, 1H), 3.00 (ddd, *J* = 14.3, 11.3, 5.7 Hz, 1H), 1.79 – 1.65 (m, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 145.1, 139.0, 135.6, 134.7, 133.5, 132.4, 129.1, 128.7, 128.1, 127.6, 121.3, 120.3, 58.6, 54.1, 52.1, 46.0, 39.4, 27.7, 24.5, 22.6, 21.7;

HRMS calculated for $C_{24}H_{30}BrN_4O_4S$ $(M+H)^+$ 549.1171, found 549.1135.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.59)



Yield 98%;

$[\alpha]_D^{25} = -51.50$ (c = 1.67, CH_2Cl_2);

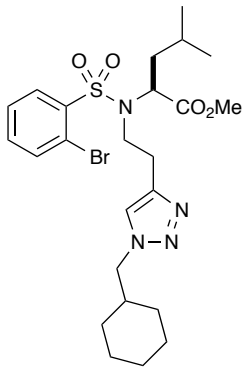
FTIR (neat): 2954, 1742, 1340, 1153 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dd, J = 7.9, 1.7 Hz, 1H), 7.72 (dd, J = 7.8, 1.3 Hz, 1H), 7.45 (dt, J = 7.6, 1.3 Hz, 1H), 7.38 (dt, J = 7.7, 1.8 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 9.5 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 5.43 (s, 2H), 4.59 (dd, J = 8.7, 5.7 Hz, 1H), 3.78 (ddd, J = 15.7, 11.3, 5.0 Hz, 1H), 3.65 (ddd, J = 15.4, 11.1, 5.7 Hz, 1H), 3.54 (s, 3H), 3.21 (ddd, J = 14.3, 11.1, 5.0 Hz, 1H), 2.99 (ddd, J = 14.3, 11.3, 5.7 Hz, 1H), 2.37 (s, 3H), 1.79 – 1.59 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 145.0, 139.0, 138.7, 135.6, 133.5, 132.4, 131.6, 129.8, 128.2, 127.5, 121.2, 120.3, 58.6, 53.9, 52.1, 46.0, 39.4, 27.7, 24.5, 22.6, 21.7, 21.2;

HRMS calculated for $C_{25}H_{32}BrN_4O_4S$ $(M+H)^+$ 563.1328, found 563.1363.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.60)



Yield 86%;

$[\alpha]_D^{25} = -55.76$ (*c* = 1.39, CH_2Cl_2);

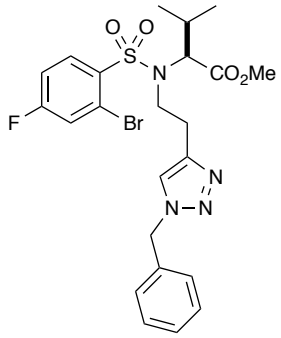
FTIR (neat): 2928, 1742, 1342, 1153 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.44 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.8 Hz, 1H), 7.34 (s, 1H), 5.31 (s, 2H), 4.58 (dd, *J* = 8.9, 5.7 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 2H), 3.81 (ddd, *J* = 15.4, 11.2, 5.0 Hz, 1H), 3.68 (ddd, *J* = 15.4, 11.1, 5.8 Hz, 1H), 3.54 (s, 3H), 3.24 (ddd, *J* = 14.3, 11.0, 5.0 Hz, 1H), 3.03 (ddd, *J* = 14.3, 11.3, 5.8 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.79 – 1.64 (m, 6H), 1.29 – 1.14 (m, 3H), 1.03 – 0.97 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 171.7, 144.4, 139.0, 135.6, 133.5, 132.5, 127.6, 121.9, 120.3, 58.6, 56.4, 52.1, 46.1, 39.4, 38.7, 30.5, 27.7, 26.1, 25.5, 24.6, 22.6, 21.7;

HRMS calculated for $C_{24}H_{36}BrN_4O_4S$ $(M+H)^+$ 555.1641, found 555.1650.

(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromo-4-fluorophenylsulfonamido)-3-methylbutanoate (4.61)



Yield 98%;

$[\alpha]_D^{25} = -33.87$ (c = 1.55, CH_2Cl_2);

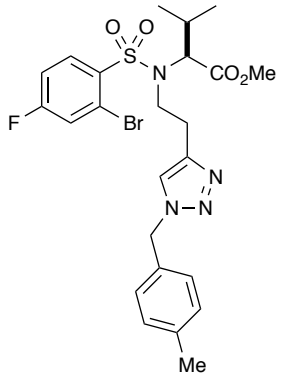
FTIR (neat): 2966, 1740, 1581, 1340, 1207, 1161, 1147 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 (dd, J = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.45 (dd, J = 2.5 Hz, $^3J_{H-F}$ = 7.9 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.31 (s, 1H), 7.30 – 7.28 (m, 2H), 7.16 (ddd, J = 9.1, 2.6 Hz, $^3J_{H-F}$ = 7.5 Hz, 1H), 5.51 (s, 2H), 3.98 (ddd, J = 15.3, 11.3, 5.7 Hz, 1H), 3.92 (d, J = 10.4 Hz, 1H), 3.85 (ddd, J = 15.4, 11.5, 4.9 Hz, 1H), 3.57 (s, 3H), 3.23 (ddd, J = 14.2, 11.4, 4.9 Hz, 1H), 3.03 (ddd, J = 14.2, 11.5, 5.7 Hz, 1H), 2.23 (dqq, J = 10.4, 6.6, 6.6 Hz, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.9, 164.1 (d, $^1J_{C-F}$ = 260.3 Hz), 145.1, 135.5 (d, $^4J_{C-F}$ = 3.8 Hz), 134.8 (d, $^3J_{C-F}$ = 8.8 Hz), 134.7, 129.1, 128.7, 128.1, 122.8 (d, $^2J_{C-F}$ = 25.2 Hz), 121.6 (d, $^3J_{C-F}$ = 10.1 Hz), 121.3, 114.8 (d, $^2J_{C-F}$ = 21.4 Hz), 65.9, 54.1, 51.7, 45.7, 28.8, 27.4, 19.9, 19.3;

HRMS calculated $C_{23}H_{27}BrFN_4O_4S$ $(M+H)^+$ 553.0920, found 553.0026.

(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.62)



Yield 88%;

$[\alpha]_D^{25} = -30.78$ (c = 1.36, CH_2Cl_2);

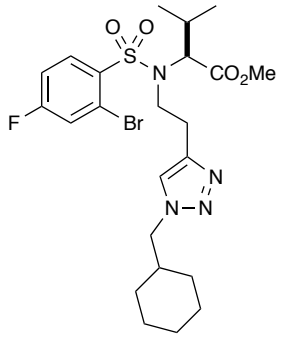
FTIR (neat): 2966, 1740, 1581, 1340, 1207, 1161, 1147, 1045 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.44 (dd, J = 2.6 Hz, $^3J_{H-F}$ = 8.0 Hz, 1H), 7.21 – 7.17 (m, 5H), 7.15 (ddd, J = 8.9, 2.5 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 5.45 (s, 2H), 3.96 (ddd, J = 15.3, 11.4, 5.7 Hz, 1H), 3.91 (d, J = 10.3 Hz, 1H), 3.83 (ddd, J = 15.2, 11.6, 4.8 Hz, 1H), 3.56 (s, 3H), 3.21 (ddd, J = 14.2, 11.5, 4.8 Hz, 1H), 3.01 (ddd, J = 14.2, 11.6, 5.7 Hz, 1H), 2.37 (s, 3H), 2.21 (dqq, J = 10.3, 6.6, 6.6 Hz, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.8, 164.1 (d, $^1J_{C-F}$ = 259.1 Hz), 145.0, 135.5 (d, $^4J_{C-F}$ = 3.8 Hz), 134.8 (d, $^3J_{C-F}$ = 8.8 Hz), 131.6, 130.0, 128.1, 122.8 (d, $^2J_{C-F}$ = 23.9 Hz), 121.7 (d, $^3J_{C-F}$ = 10.1 Hz), 121.2, 114.8 (d, $^2J_{C-F}$ = 22.6 Hz), 65.9, 53.9, 51.7, 45.7, 30.9, 28.8, 27.5, 21.2, 19.9, 19.3;

HRMS calculated $C_{24}H_{29}BrFN_4O_4S$ $(M+H)^+$ 567.1077, found 567.1023.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.63)



Yield 98%;

$[\alpha]_D^{25} = -29.23$ (c = 1.37, CH_2Cl_2);

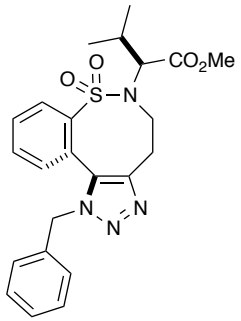
FTIR (neat): 2928, 1740, 1582, 1465, 1340, 1207, 1163, 1148, 1047 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (dd, J = 8.9 Hz, $^4J_{H-F}$ = 5.8 Hz, 1H), 7.46 (dd, J = 2.5 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 7.34 (s, 1H), 7.17 (ddd, J = 8.9, 2.5 Hz, $^3J_{H-F}$ = 7.4 Hz, 1H), 4.14 (d, J = 7.2 Hz, 2H), 4.00 (ddd, J = 15.3, 11.3, 5.8 Hz, 1H), 3.91 (d, J = 10.3 Hz, 1H), 3.87 (ddd, J = 15.5, 11.5, 4.9 Hz, 1H), 3.57 (s, 3H), 3.24 (ddd, J = 14.2, 11.4, 4.9 Hz, 1H), 3.05 (ddd, J = 14.1, 11.5, 5.8 Hz, 1H), 2.37 (dqq, J = 9.6, 6.6, 6.6 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.76 – 1.61 (m, 5H), 1.28 – 1.14 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H),1.00 – 0.95 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.9, 164.1 (d, $^1J_{C-F}$ = 260.3 Hz), 144.4, 135.5 (d, $^4J_{C-F}$ = 3.8 Hz), 134.8 (d, $^3J_{C-F}$ = 8.8 Hz), 122.8 (d, $^2J_{C-F}$ = 25.2 Hz), 121.8, 121.7 (d, $^3J_{C-F}$ = 11.3 Hz), 114.8 (d, $^2J_{C-F}$ = 21.4 Hz), 65.9, 56.4, 51.8, 45.9, 38.8, 30.9, 30.5, 28.8, 27.5, 26.1, 25.5, 19.9, 19.3;

HRMS calculated $C_{23}H_{33}BrFN_4O_4S$ $(M+H)^+$ 559.1390, found 559.1349.

(*S*)-Methyl 2-(1-benzyl-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.64)



Yield 25%;

Mp 136 ºC;

$[\alpha]_D^{25} = -27.08$ ($c = 0.65$, CH_2Cl_2);

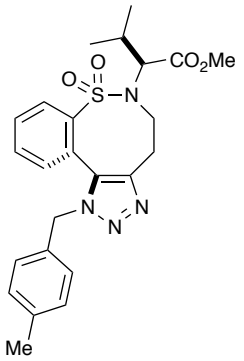
FTIR (neat): 2965, 1750, 1348, 1168 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 7.8, 1.3 Hz, 1H), 7.62 (dt, J = 7.6, 1.3 Hz, 1H), 7.56 (dt, J = 7.5, 1.5 Hz, 2H), 7.28 – 7.26 (m, 3H), 7.20 (dd, J = 7.1, 1.3 Hz, 1H), 7.08 (dd, J = 7.2, 3.4 Hz, 1H), 5.54 (d, J = 15.4 Hz, 1H), 5.33 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 3.68 (dd, J = 14.9, 11.3 Hz, 1H), 3.53 (ddd, J = 13.1, 5.3, 1.9 Hz, 1H), 3.21 (dd, J = 14.8, 4.5 Hz, 1H), 3.19 (s, 3H), 2.27 – 2.20 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.7, 144.9, 142.4, 134.9, 132.9, 131.5, 131.3, 130.1, 129.7, 128.7, 128.2, 127.5, 123.8, 64.8, 52.4, 51.6, 42.2, 27.4, 26.1, 19.2, 18.6;

HRMS calculated for $C_{23}H_{26}N_4O_4SNa$ $(M+Na)^+$ 477.1572, found 477.1577.

(*S*)-Methyl 3-methyl-2-(1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)butanoate (4.65)



Yield 37%;

$[\alpha]_D^{25} = -50.16$ (c = 1.29, CH_2Cl_2);

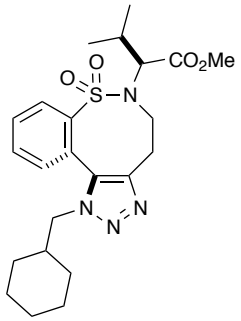
FTIR (neat): 2966, 1740, 1342, 1160 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 (dd, J = 6.8, 1.2 Hz, 1H), 7.63 (dt, J = 7.7, 1.4 Hz, 1H), 7.56 (dt, J = 7.6, 1.4 Hz, 1H), 7.21 (dd, J = 7.6, 1.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 5.51 (d, J = 15.3 Hz, 1H), 5.26 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 3.67 (dd, J = 14.8, 11.3 Hz, 1H), 3.53 (ddd, J = 14.8, 5.4, 1.8 Hz, 1H), 3.22 (dd, J = 15.4, 4.7 Hz, 1H), 3.18 (s, 3H), 2.30 (s, 3H), 2.25 – 2.19 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.6, 144.8, 142.3, 138.0, 132.8, 131.9, 131.5, 131.0, 130.1, 129.7, 129.3, 127.4, 123.8, 64.8, 52.1, 51.6, 42.2, 27.4, 26.0, 21.1, 19.2, 18.6;

HRMS calculated for $C_{24}H_{29}N_4O_4S$ $(M+H)^+$ 469.1910, found 469.1914.

(*S*)-Methyl 2-(1-(cyclohexylmethyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.66)



Yield 40%;

$[\alpha]_D^{25}$ = –42.37 (*c* = 1.56, CH_2Cl_2);

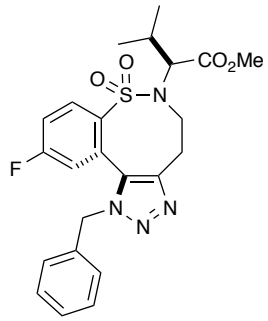
FTIR (neat): 2964, 2926, 1740, 1346, 1167 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.28 – 8.23 (m, 1H), 7.70 – 7.65 (m, 2H), 7.42 – 7.38 (m, 1H), 4.18 (dd, *J* = 13.6, 8.5 Hz, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.00 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.69 (dd, *J* = 14.9, 11.2 Hz, 1H), 3.54 (ddd, *J* = 14.8, 5.4, 1.7 Hz, 1H), 3.22 (s, 3H), 3.21 (dd, *J* = 15.4, 4.9 Hz, 1H), 2.27 – 2.17 (m, 2H), 1.70 – 1.48 (m, 5H), 1.15 – 1.07 (m, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.91 – 0.75 (m 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.7, 144.7, 142.2, 132.6, 131.8, 130.9, 130.3, 129.6, 124.5, 64.9, 54.9, 51.6, 42.2, 37.8, 30.4, 30.3, 29.7, 27.4, 26.1, 25.4, 25.3, 19.3, 18.6;

HRMS calculated for $C_{23}H_{33}N_4O_4S$ $(M+H)^+$ 461.2223, found 461.2175.

(*S*)-Methyl 2-(1-benzyl-10-fluoro-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.67)



Yield 54%;

$[\alpha]_D^{25} = -17.36$ ($c = 2.35$, CH_2Cl_2);

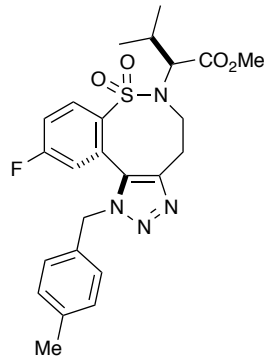
FTIR (neat): 2966, 1740, 1581, 1346, 1160, 1144 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 8.9 Hz, $^4J_{H-F}$ = 5.5 Hz, 1H), 7.30 – 7.27 (m, 5H), 7.10 (dd, J = 3.5, 7.2 Hz, 1H), 6.84 (dd, J = 2.5 Hz, $^3J_{H-F}$ = 8.6 Hz, 1H), 5.58 (d, J = 15.4 Hz, 1H), 5.34 (d, J = 15.5 Hz, 1H), 3.9 (d, J = 10.9 Hz, 1H), 3.66 (dd, J = 14.9, 1.2 Hz, 1H), 3.56 – 3.51 (m, 1H), 3.27 (s, 3H), 3.23 (dd, J = 15.8, 5.0 Hz, 1H), 2.27 – 2.21 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.2, 163.2 (d, $^1J_{C-F}$ = 256.6 Hz), 145.1, 138.6 (d, $^4J_{C-F}$ = 3.8 Hz), 134.6, 132.8 (d, $^3J_{C-F}$ = 10.1 Hz), 128.8, 128.7, 128.4 127.5, 126.6 (d, $^3J_{C-F}$ = 10.1 Hz), 118.4 (d, $^2J_{C-F}$ = 23.9 Hz), 116.5 (d, $^2J_{C-F}$ = 21.4 Hz), 64.9, 52.7, 51.7, 42.2, 27.5, 26.0, 19.2, 18.6;

HRMS calculated for $C_{23}H_{26}FN_4O_4S$ $(M+H)^+$ 473.1659, found 473.1904.

(*S*)-Methyl 2-(10-fluoro-1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.68)



Yield 45%;

$[a]_D^{25} = -27.94$ (c = 1.80, CH_2Cl_2);

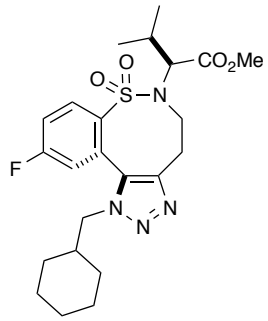
FTIR (neat): 2970, 1740, 1582, 1346, 1161 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 9.0 Hz, $^4J_{H-F}$ = 5.5 Hz, 1H), 7.28 (ddd, J = 9.0, 2.6 Hz, $^3J_{H-F}$ = 7.6 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.84 (dd, J = 2.6 Hz, $^3J_{H-F}$ = 8.6 Hz, 1H), 5.54 (d, J = 15.3 Hz, 1H), 5.27 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 3.66 (dd, J = 14.8, 11.2 Hz, 1H), 3.54 (ddd, J = 14.9, 7.4, 1.8 Hz, 1H), 3.27 (s, 3H), 3.23 (dd, J = 15.4, 4.6 Hz, 1H), 2.31 (s, 3H), 2.26 – 2.20 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.6, 163.2 (d, $^1J_{C-F}$ = 255.3 Hz), 145.0, 138.6 (d, $^4J_{C-F}$ = 3.8 Hz), 138.2, 132.8 (d, $^3J_{C-F}$ = 8.8 Hz), 131.7, 129.8, 129.5, 127.4, 126.6 (d, $^3J_{C-F}$ = 10.1 Hz), 118.5 (d, $^2J_{C-F}$ = 23.9 Hz), 116.5 (d, $^2J_{C-F}$ = 22.6 Hz), 64.9, 52.4, 51.7, 42.3, 27.5, 26.0, 21.1, 19.2, 18.6;

HRMS calculated for $C_{24}H_{28}FN_4O_4S$ $(M+H)^+$ 487.1815, found 487.1811.

(*S*)-Methyl 2-(1-(cyclohexylmethyl)-10-fluoro-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.69)



Yield 48%;

$[\alpha]_D^{25} = -22.39$ (c = 1.80, CH_2Cl_2);

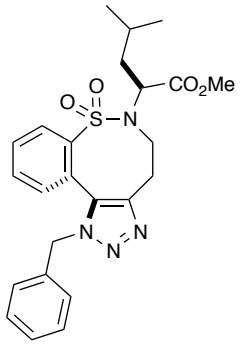
FTIR (neat): 2925, 1740, 1448, 1348, 1169 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (dd, J = 9.0 Hz, $^4J_{H-F}$ = 5.6 Hz, 1H), 7.35 (ddd, J = 9.0, 2.6 Hz, $^3J_{H-F}$ = 7.7 Hz, 1H), 7.10 (dd, J = 2.7 Hz, $^3J_{H-F}$ = 8.5 Hz, 1H), 4.21 (dd, J = 13.6, 8.5 Hz, 1H), 4.06 (d, J = 10.9 Hz, 1H), 4.01 (dd, J = 13.6, 6.3 Hz, 1H), 3.67 (dd, J = 14.9, 11.0 Hz, 1H), 3.56 (ddd, J = 14.9, 5.3, 1.8 Hz, 1H), 3.31 (s, 3H), 3.23 (dd, J = 15.4, 4.8 Hz, 1H), 2.29 – 2.18 (m, 2H), 7.71 – 1.52 (m, 7H), 1.16 – 1.09 (m, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.85 – 0.78 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.6, 163.5 (d, $^1J_{C-F}$ = 256.6 Hz), 144.9, 138.5 (d, $^4J_{C-F}$ = 2.5 Hz), 133.1 (d, $^3J_{C-F}$ = 8.8 Hz), 131.6, 127.3 (d, $^3J_{C-F}$ = 8.8 Hz), 117.8 (d, $^2J_{C-F}$ = 23.9 Hz), 116.5 (d, $^2J_{C-F}$ = 21.4 Hz), 65.0, 55.0, 51.7, 42.2, 37.9, 30.4, 30.3, 27.5, 26.0, 25.4, 19.2, 18.6;

HRMS calculated for $C_{23}H_{32}FN_4O_4S$ $(M+H)^+$ 479.2128, found 479.2090.

(*S*)-Methyl 2-(1-benzyl-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.70)



Yield 50%;

FTIR (neat): 2955, 2934, 1741, 1344, 1170, 1153 cm^{-1};

HRMS calculated for $C_{24}H_{28}N_4O_4SNa$ $(M+Na)^+$ 491.1729, found 491.1735.

Major Isomer

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.55 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.27 (m, 3H), 7.21 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.08 (dd, *J* = 7.4, 3.7 Hz, 2H), 5.55 (d, *J* = 15.4 Hz, 1H), 5.33 (d, *J* = 15.4 Hz, 1H), 4.60 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.67 (dd, *J* = 15.0, 11.3 Hz, 1H), 3.49 (ddd, *J* = 15.1, 5.2, 1.8 Hz, 1H), 3.25 (s, 3H), 3.22 (dd, *J* = 15.3, 5.0 Hz, 1H), 2.55 (ddd, *J* = 15.2, 11.5, 1.9 Hz, 1H), 1.75 – 1.59 (m, 3H), 0.99 (d, *J* = 6.1 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H);

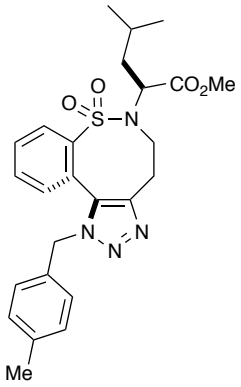
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.3, 145.0, 142.2, 135.0, 132.9, 132.1, 131.4, 130.0, 129.6, 128.6, 128.1, 127.5, 124.1, 57.6, 52.4, 51.8, 42.2, 38.8, 26.2, 24.3, 22.9, 21.7.

Minor Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 6.4, 1.3 Hz, 1H), 7.55 (m, 2H), 7.27 (m, 3H), 7.22 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.08 (m, 2H), 5.54 (d, *J* = 15.4 Hz, 1H), 5.30 (d, *J* = 15.4 Hz, 1H), 4.52 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.81 (dd, *J* = 15.3, 11.8 Hz, 1H), 3.76 (s, 3H), 3.53 (ddd, *J* = 15.3, 5.0, 1.8 Hz, 1H), 3.38 (dd, *J* = 15.2, 4.5 Hz, 1H), 2.36 (ddd, *J* = 14.9, 11.9, 1.8 Hz, 1H), 1.20 (ddd, *J* = 14.1, 8.7, 5.4 Hz, 1H), 0.93 – 0.87 (m, 2H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 144.4, 142.3, 134.9, 132.7, 131.7, 131.5, 130.0, 129.7, 128.7, 128.2, 127.4, 123.9, 59.1, 52.6, 52.4, 43.2, 39.2, 28.3, 24.7, 22.3, 22.2.

(*S*)-Methyl 4-methyl-2-(1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)pentanoate (4.71)



Yield 28%;

FTIR (neat): 2960, 1742, 1344, 1169, 1151 cm^{-1};

HRMS calculated for $C_{25}H_{30}N_4O_4SNa$ $(M+Na)^+$ 505.1885, found 505.1880.

Major Isomer

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.55 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.22 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 5.52 (d, *J* = 15.4 Hz, 1H), 5.26 (d, *J* = 15.4 Hz, 1H), 4.60 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.53 (ddd, *J* = 15.4, 5.2, 1.9 Hz, 1H), 3.66 (dd, *J* = 15.0, 11.4 Hz, 1H), 3.24 (s, 3H), 3.22 (dd, *J* = 15.5, 4.8 Hz, 1H), 2.54 (ddd, *J* = 15.2, 11.4, 1.8 Hz, 1H), 2.31 (s, 3H), 1.73 – 1.61 (m, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H);

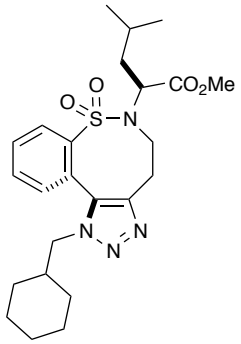
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.3, 145.0, 142.2, 137.9, 132.9, 132.2, 131.7, 131.6, 130.0, 129.7, 128.7, 127.4, 124.1, 57.6, 52.2, 52.1, 42.3, 38.8, 26.2, 24.3, 22.9, 21.7, 21.1.

Minor Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (dd, *J* = 6.5, 1.5 Hz, 1H), 7.60 (dt, J = 7.6, 1.5 Hz, 1H), 7.27 – 7.53 (m, 1H), 7.23 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.50 (d, *J* = 15.3 Hz, 1H), 5.23 (d, *J* = 15.2 Hz, 1H), 4.53 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.81 (dd, *J* = 15.6, 11.7 Hz, 1H), 3.76 (s, 3H), 3.49 (ddd, *J* = 15.1, 5.3, 1.8 Hz, 1H), 3.37 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.37 (ddd, *J* = 13.5, 7.6, 1.8 Hz, 1H), 2.31 (s, 3H), 1.20 (ddd, *J* = 13.4, 8.7, 5.4 Hz, 1H), 0.94 – 0.87 (m, 2H), 0.71 (d, *J* = 6.2 Hz, 3H), 0.69 (d, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 144.3, 142.7, 138.0, 132.6, 132.0, 131.9, 131.5, 130.0, 129.7, 128.7, 127.3, 123.9, 59.1, 52.6, 51.8, 43.3, 39.2, 28.3, 24.7, 22.3, 22.2.

(*S*)-Methyl 2-(1-(cyclohexylmethyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.72)



Yield 38%;

FTIR (neat): 2926, 2853, 1742, 1344, 1169, 1151 cm^{-1};

HRMS calculated for $C_{24}H_{34}N_4O_4SNa$ $(M+Na)^+$ 497.2198, found 497.2195.

Major Isomer

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.42 (dd, *J* = 7.1, 1.4 Hz, 1H), 4.66 (dd, *J* = 8.6, 6.0 Hz, 1H), 4.18 (dd, *J* = 13.6, 8.5 Hz, 1H), 4.01 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.67 (dd, *J* = 14.9, 11.2 Hz, 1H), 3.53 – 3.50 (m, 1H), 3.28 (s, 3H), 3.20 (dd, *J* = 15.1, 4.9 Hz, 1H), 2.53 (ddd, *J* = 15.2, 11.4, 1.8 Hz, 1H), 1.73 – 1.52 (m, 7H), 1.15 – 1.05 (m, 4H), 1.01 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.94 – 0.87 (m, 3H);

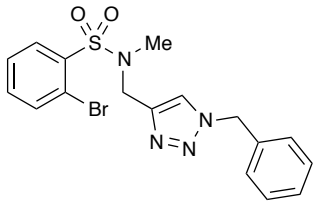
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 144.9, 142.0, 132.6, 131.8, 131.0, 129.9, 129.6, 124.7, 57.7, 54.9, 51.9, 42.2, 38.8, 37.7, 30.4, 30.3, 26.1, 25.4, 25.3, 24.3, 23.0, 21.7.

Minor Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.20 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.44 (dd, *J* = 6.8, 1.4 Hz, 1H), 4.58 (dd, *J* = 8.6, 6.4 Hz, 1H), 4.17 (dd, *J* = 13.7, 8.5 Hz, 1H), 3.98 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.81 (dd, *J* = 15.4, 11.6 Hz, 1H), 3.77 (s, 3H), 3.53 – 3.50 (m, 1H), 3.36 (dd, *J* = 15.3, 5.0 Hz, 1H), 2.34 (ddd, *J* = 15.1, 11.7, 1.7 Hz, 1H), 1.73 – 1.52 (m, 7H), 1.15 – 1.05 (m, 4H), 0.94 – 0.87 (m, 3H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.972 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 144.3, 142.5, 132.4, 131.9, 131.6, 129.8, 128.9, 124.4, 59.2, 54.9, 52.7, 43.2, 39.2, 37.8, 30.3, 28.3, 26.2, 24.5, 25.2, 24.8, 22.4, 22.2.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-methylbenzenesulfonamide (4.73)**



Yield 98%;

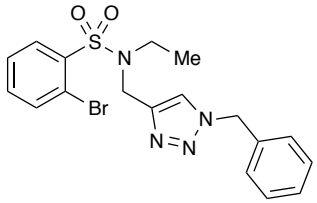
FTIR (neat): 3137, 2935, 1574, 1447, 1331, 1159, 913, 748 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (s, 1H), 7.44 (td, *J* = 7.7, 1.4 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.29 – 7.25 (m, 2H), 5.52 (s, 2H), 4.56 (s, 2H), 2.87 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.0, 138.4, 125.7, 134.4, 133.6, 132.2, 129.2, 128.8, 128.1, 127.5, 122.9, 120.4, 54.3, 45.3, 34.5;

HRMS calculated for $C_{17}H_{17}BrN_4O_2SNa$ $(M+Na)^+$ 443.0153, found 4430151.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-ethylbenzenesulfonamide (4.74)**



Yield 86%;

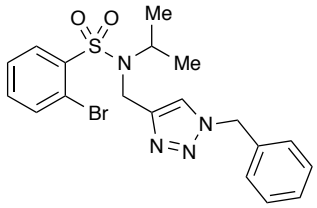
FTIR (neat): 3280, 296, 1574, 1447, 1331, 1155, 1029, 750 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.65 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (s, 1H), 7.43 – 7.32 (m, 5H), 7.28 – 7.23 (m, 2H), 5.50 (s, 2H), 4.65 (s, 2H), 3.34 (q, *J* = 7.1 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.6, 139.4, 135.6, 134.5, 133.5, 132.1, 129.1, 128.8, 128.1, 128.0, 127.5, 123.0, 120.5, 54.2, 42.0, 41.8, 13.1;

HRMS calculated for $C_{19}H_{19}BrN_4O_2SNa$ $(M+Na)^+$ 469.0310, found 469.0338.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-isopropylbenzenesulfonamide (4.75)**



Yield 98%;

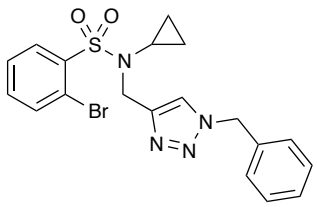
FTIR (neat): 2980, 1448, 1329, 1153, 1047, 761 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.63 (s, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 – 7.34 (m, 4H), 7.26 – 7.21 (m, 2H), 5.50 (s, 2H), 4.70 (s, 2H), 3.96 (hept, *J* = 6.8 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 147.1, 139.2, 135.5, 134.7, 133.5, 132.5, 129.1, 128.7, 127.8, 127.5, 123.5, 120.2, 54.1, 49.9, 38.6, 21.0;

HRMS calculated for $C_{19}H_{21}BrN_4O_2SNa$ $(M+Na)^+$ 471.0466, found 471.0473.

***N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-cyclopropylbenzenesulfonamide (4.76)**



Yield 82%;

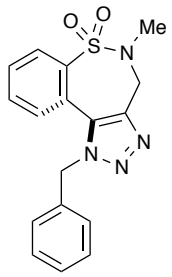
FTIR (neat): 3285, 2955, 1448, 1329, 1159, 912, 744 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.71 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.70 (s, 1H), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H), 7.43 – 7.34 (m, 4H), 7.30 – 7.26 (m, 2H), 5.55 (s, 2H), 4.79 (s, 2H), 2.52 – 2.43 (m, 1H), 0.64 – 0.53 (m, 2H), 0.42 – 0.34 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.8, 139.7, 135.5, 134.6, 133.7, 132.3, 129.1, 128.7, 128.0, 127.5, 123.3, 120.4, 54.2, 45.9, 29.3, 7.2;

HRMS calculated for $C_{18}H_{19}BrN_4O_2SNa$ $(M+Na)^+$ 457.0310, found 457.0351.

(±)-1-Benzyl-5-methyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.77)



Yield 78%;

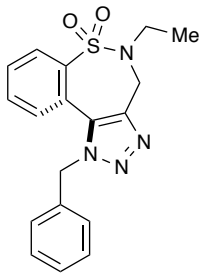
FTIR (neat): 2934, 1697, 1454, 1343, 1166, 913 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.55 (td, *J* = 7.5, 1.7 Hz, 1H), 7.52 (td, *J* = 7.5, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.36 – 7.32 (m, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 5.70 (s, 2H), 4.82 (s, 2H), 2.74 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.9, 138.2, 135.2, 132.6, 131.3, 130.2, 129.3, 129.2, 129.0, 128.4, 126.5, 123.7, 53.2, 49.5, 37.7;

HRMS calculated for $C_{17}H_{16}N_4O_2SNa$ $(M+Na)^+$ 363.0892, found 363.0875.

(±)-1-Benzyl-5-ethyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.78)



Yield 80%;

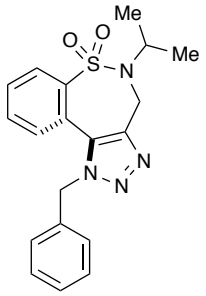
FTIR (neat): 2985, 1699, 1454, 1340, 1164, 1132, 912, 752 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.13 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.53 (td, *J* = 7.6, 1.7 Hz, 1H), 7.49 (td, *J* = 7.6, 1.5 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.38 (ddd, *J* = 7.6, 6.3, 1.6 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.70 (s, 2H), 4.85 (d, *J* = 1.2 Hz, 2H), 3.04 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 142.3, 140.2, 135.2, 132.4, 131.5, 129.4, 129.3, 129.2, 128.9, 128.3, 126.5, 123.7, 53.2, 46.1, 45.0, 13.5;

HRMS calculated for $C_{18}H_{18}N_4O_2SNa$ $(M+Na)^+$ 377.1048, found 377.1051.

(±)-1-Benzyl-5-isopropyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.79)



Yield 88%;

Mp 184 ºC;

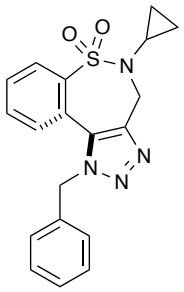
FTIR (neat): 2983, 1339, 1160, 1048, 752 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.12 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 (td, *J* = 7.6, 1.6 Hz, 1H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.36 – 7.31 (m, 1H), 7.22 (d, *J* = 7.1 Hz, 2H), 5.69 (s, 2H), 4.82 (s, 2H), 3.98 (hept, *J* = 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.1, 141.6, 135.2, 132.3, 131.6, 129.2, 129.1, 128.8, 128.7, 128.3, 126.5, 124.0, 53.2, 49.8, 40.4, 20.2;

HRMS calculated for $C_{19}H_{20}N_4O_2SNa$ $(M+Na)^+$ 391.1205, found 391.1189.

(±)-1-Benzyl-5-cyclopropyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.80)



Yield 72%;

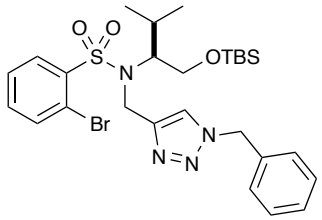
FTIR (neat): 2979, 1454, 1346, 1172, 1135, 912, 736 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.21 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.39 (td *J* = 7.7, 1.6 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 5.72 (s, 2H), 4.93 (s, 2H), 1.81 (hept, *J* = 3.4 Hz, 1H), 1.00 – 0.91 (m, 2H), 0.67 – 0.54 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 142.6, 138.4, 135.2, 132.7, 131.1, 130.5, 129.23 129.2, 129.0, 128.3, 126.5, 123.7, 53.3, 49.8, 31.9, 7.9;

HRMS calculated for $C_{18}H_{18}N_4O_2SNa$ $(M+Na)^+$ 377.1048, found 377.1047.

(*S*)-*N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-(1-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-yl)benzenesulfonamide (4.81)



Yield 84%;

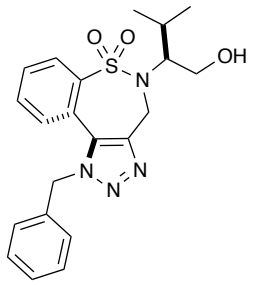
FTIR (neat): 2955, 2927, 2856, 1464, 1335, 1256, 1157, 1099, 1053, 837 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.08 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.67 (s, 1H), 7.39 – 7.30 (m, 5H), 7.26 – 7.23 (m, 2H), 5.52 – 5.41 (m, 2H), 4.96 (d, *J* = 16.4 Hz, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 3.71 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.61 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.37 (dt, *J* = 10.0, 4.0 Hz, 1H), 2.19 – 2.11 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.83 (s, 9H), 0.67 (d, *J* = 6.7 Hz, 3H), -0.06 (d, *J* = 5.7 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 146.3, 140.2, 135.6, 134.7, 133.2, 132.2, 129.0, 128.6, 127.9, 127.5, 123.8, 119.9, 65.7, 63.8, 54.1, 41.3, 27.9, 25.8, 20.4, 19.8, 18.1, -5.7, -5.8;

HRMS calculated for $C_{27}H_{39}BrN_4O_3SSiNa$ $(M+Na)^+$ 629.1593, found 629.1598.

(*S*)-1-Benzyl-5-((*S*)-1-hydroxy-3-methylbutan-2-yl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.82)



Yield 47%;

$[\alpha]_D^{25}$ = +3.14 (*c* = 3.19, CH_2Cl_2);

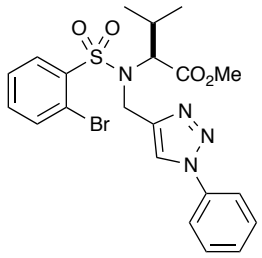
FTIR (neat): 3335, 2964, 1437, 1339, 1159, 1132, 1049 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.04 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.6 Hz, 1H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.35 – 7.30 (m, 1H), 7.21(d, *J* = 7.1 Hz, 2H), 5.73 (d, *J* = 16.1 Hz, 1H), 5.65 (d, *J* = 16.1 Hz, 1H), 4.89 (d, *J* = 16.1 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 3.67 – 3.54 (m, 3H), 1.94 – 1.84 (m, 1H), 1.22 (t, *J* = 5.1 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 142.6, 142.3, 135.2, 132.0, 131.7, 129.1, 129.0, 128.7, 128.3, 127.5, 126.5, 123.7, 66.4, 61.3, 53.0, 42.1, 27.7, 20.2, 20.0;

HRMS calculated for $C_{21}H_{25}N_4O_3S$ $(M+H)^+$ 413.1647, found 413.1656.

(*S*)-Methyl 2-(2-bromo-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.83)



Yield 21%;

$[\alpha]_D^{25}$ = +7.80 (*c* = 2.30, CH_2Cl_2);

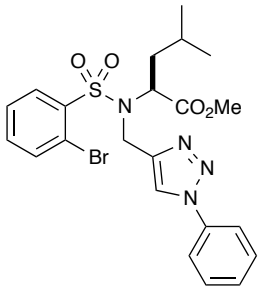
FTIR (neat): 3062, 2966, 1738, 1601, 1502, 1434, 1339, 1161, 1149, 1037, 760 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (s, 1H), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.74 – 7.68 (m, 3H), 7.53 (dd, *J* = 10.6, 5.0 Hz, 2H), 7.43 (m, 2H), 7.35 (td, *J* = 7.6, 1.7 Hz, 1H), 5.24 – 5.10 (m, 2H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.50 (s, 3H), 2.46 (dqq, *J* = 10.5, 6.6, 6.6 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.8, 146.0, 139.1, 137.0, 135.3, 133.6, 132.9, 129.7, 128.7, 127.6, 122.3, 120.5, 120.1, 66.1, 51.7, 41.2, 28.7, 19.8, 19.2;

HRMS calculated for $C_{21}H_{23}BrN_4O_4SNa$ $(M+Na)^+$ 529.0521, found 529.0521.

(*S*)-Methyl 2-(2-bromo-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.84)



Yield 78%;

$[\alpha]_D^{25} = -55.53$ (c = 1.50, CH_2Cl_2);

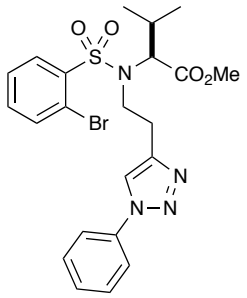
FTIR (neat): 2955, 1742, 1599, 1501, 1448, 1344, 1155, 1040, 757 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.24 (s, 1H), 8.13 (dd, J = 7.9, 1.7 Hz, 1H), 7.77 –7.70 (m, 3H), 7.57 – 7.52 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 – 7.35 (m, 1H), 5.02 (d, J = 16.8 Hz, 1H), 4.82 (d, J = 16.8 Hz, 1H), 4.69 (dd, J = 10.2, 4.8 Hz, 1H), 3.55 (s, 3H), 1.90 (ddd, J = 14.3, 10.3, 4.2 Hz, 1H), 1.67 (ddd, J = 14.2, 9.4, 4.8 Hz, 1H), 1.47 – 1.39 (m, 1H), 0.91 (d, J = 6.5 Hz, 3H), 0.68 (d, J = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.5, 146.2, 139.1, 137.0, 135.6, 133.6, 132.3, 129.7, 128.8, 127.6, 122.4, 120.6, 120.2, 58.9, 52.2, 41.6, 39.3, 24.4, 22.4, 21.3;

HRMS calculated for $C_{22}H_{26}BrN_4O_4S$ $(M+H)^+$ 521.0858, found 521.0854.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.85)



Yield 90%;

$[\alpha]_D^{25} = -30.68$ ($c = 4.00$, CH_2Cl_2);

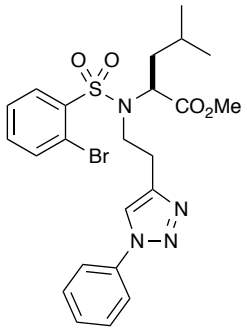
FTIR (neat): 2966, 2952, 1741, 1599, 1502, 1342, 1163, 1149, 1045, 757 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.18 (dd, J = 7.9, 1.7 Hz, 1H), 7.85 (s, 1H), 7.75 – 7.70 (m, 3H), 7.55 – 7.51 (m, 2H), 7.48 (dt, J = 7.9, 1.3 Hz, 1H), 7.44 (tt, J = 7.9, 1.0 Hz, 1H), 7.40 (td, J = 7.9, 1.7 Hz, 1H), 4.08 (ddd, J = 15.1, 11.1, 5.8 Hz, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.96 (ddd, J = 15.1, 11.1, 5.8 Hz, 1H), 3.56 (s, 3H), 3.35 (ddd, J = 14.3, 11.1, 4.8 Hz, 1H), 3.16 (ddd, J = 11.3, 11.2, 5.8 Hz, 1H), 2.26 (dqq, J = 13.1, 10.3, 6.6 Hz, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.0, 145.5, 139.1, 137.1, 135.5, 133.7, 132.8, 129.7, 128.6, 127.6, 120.5, 120.3, 119.8, 65.9, 51.7, 45.8, 28.9, 27.5, 19.9, 19.3;

HRMS calculated for $C_{22}H_{25}BrN_4O_4SNa$ $(M+Na)^+$ 543.0678, found 543.0675.

(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.86)



Yield 95%;

$[\alpha]_D^{25}$ = –60.65 (*c* = 5.00, CH_2Cl_2);

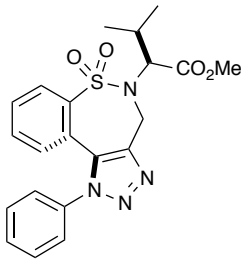
FTIR (neat): 2955, 1740, 1500, 1344, 1153, 1045, 760 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.85 (s, 1H), 7.76 – 7.70 (m, 3H), 7.56 – 7.50 (m, 2H), 7.49 – 7.42 (m, 2H), 7.39 (td, *J* = 7.5, 1.7 Hz, 1H), 4.60 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.88 (ddd, *J* = 15.8, 10.9, 5.1 Hz, 1H), 3.76 (ddd, *J* = 15.6, 10.6, 5.9 Hz, 1H), 3.55 (s, 3H), 3.34 (ddd, *J* = 14.7, 10.6, 5.0 Hz, 1H), 3.14 (ddd, *J* = 14.3, 10.8, 6.0 Hz, 1H), 1.84 – 1.66 (m, 3H), 0.94 (d, *J* = 5.9 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 145.4, 138.9, 137.1, 135.6, 133.6, 132.5, 129.7, 128.6, 127.6, 120.5, 120.4, 119.9, 58.6, 52.2, 46.1, 39.5, 27.7, 24.6, 22.7, 21.7;

HRMS calculated for $C_{23}H_{27}BrN_4O_4SNa$ $(M+Na)^+$ 557.0834, found 557.0813.

(2*S*)-Methyl 2-(6,6-dioxido-1-phenyl-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.87)



Yield 60%;

Mp 170 ºC;

$[\alpha]_D^{25} = -3.60$ (*c* = 2.50, CH_2Cl_2);

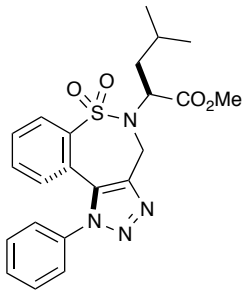
FTIR (neat): 2966, 2934, 1737, 1597, 1501, 1436, 1350, 1159, 995, 914, 764 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.44 – 7.34 (m, 3H), 7.31 – 7.24 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.21 – 5.02 (m, 2H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.11 (s, 3H), 2.20 (dqq, *J* = 10.5, 6.6, 6.6 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.4, 143.1, 140.5, 136.9, 131.8, 130.6, 130.1, 129.7, 129.7, 128.6, 128.2, 125.9, 123.9, 65.2, 51.8, 43.0, 29.0, 19.3, 19.1;

HRMS calculated for $C_{21}H_{22}FN_4O_4S$ $(M+H)^+$ 449.1259, found 449.1261.

(2*S*)-Methyl 2-(6,6-dioxido-1-phenyl-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.88)



Yield 46%;

$[\alpha]_D^{25}$ = +1.36 (*c* = 2.20, CH_2Cl_2);

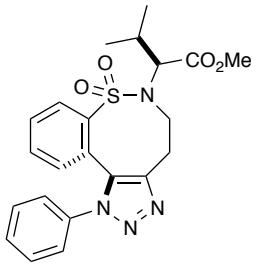
FTIR (neat): 2957, 2931, 1742, 1500, 1436, 1348, 1161, 995, 761 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.41 – 7.35 (m, 3H), 7.29 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.01 (d, *J* = 16.3 Hz, 1H), 4.94 (d, *J* = 16.3 Hz, 1H), 4.55 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.32 (s, 3H), 1.74 – 1.60 (m, 2H), 0.93 (t, *J* = 6.0 Hz, 5H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.2, 142.9, 140.8, 136.8, 131.8, 130.7, 130.5, 129.7, 128.2, 128.0, 125.9, 124.2, 58.1, 52.1, 43.0, 38.8, 24.6, 23.0, 21.0;

HRMS calculated for $C_{22}H_{24}N_4O_4SNa$ $(M+Na)^+$ 463.1416, found 463.1413.

(*S*)-Methyl 2-(7,7-dioxido-1-phenyl-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.89)



Yield 44%;

Mp 135 ºC;

$[\alpha]_D^{25} = -3.20$ (c = 2.10, CH_2Cl_2);

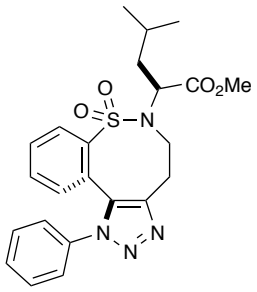
FTIR (neat): 2968, 1738, 1504, 1435, 1344, 1163, 983, 750 cm^{-1};

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.22 (dd, J = 8.1, 1.2 Hz, 1H), 7.55 (td, J = 7.8, 1.3 Hz, 1H), 7.42 – 7.29 (m, 6H), 6.99 (dd, J = 7.7, 1.3 Hz, 1H), 4.14 (d, J = 10.9 Hz, 1H), 3.78 (dd, J = 15.1, 11.3 Hz, 1H), 3.64 (ddd, J = 14.9, 5.6, 1.8 Hz, 1H), 3.31 (dd, J = 15.3, 5.5 Hz, 1H), 3.24 (s, 3H), 2.37 – 2.24 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.7, 145.1, 141.9, 136.3, 133.1, 131.8, 131.6, 129.9, 129.4, 129.3, 129.1, 125.1, 124.4, 65.0, 51.6, 42.1, 27.5, 26.1, 19.3, 18.7;

HRMS calculated for $C_{22}H_{24}N_4O_4SNa$ $(M+Na)^+$ 463.1416, found 463.1405.

(*S*)-Methyl 2-(7,7-dioxido-1-phenyl-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.90)



Yield 44%;

FTIR (neat): 3007, 2882, 1742, 1506, 1342, 1239, 1169, 1151, 993, 917, 742 cm^{-1};

HRMS calculated for $C_{23}H_{26}N_4O_4SNa$ $(M+Na)^+$ 477.1572, found 477.1570.

Major Isomer

^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.19 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.54 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.39 (dd, *J* = 3.4, 1.4 Hz, 1H), 7.43 – 7.30 (m, 5H), 7.02 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.72 (t, *J* = 7.5 Hz, 1H), 3.77 (dd, *J* = 15.4, 11.4 Hz, 1H), 3.61 (ddd, *J* = 15.1, 5.6, 1.8 Hz, 1H), 3.33 (m, *J* = 15.3, 5.4 Hz, 1H), 3.30 (s, 3H), 2.65 (ddd, *J* = 15.4, 11.3, 1.8 Hz, 1H), 1.80 – 1.76 (m, 2H), 1.75 – 1.66 (m, 1H), 1.05 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H);

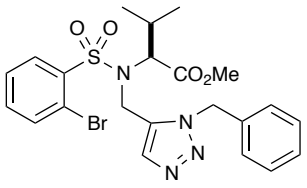
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.4, 145.2, 141.8, 136.3, 133.3, 131.9, 131.6, 129.5, 129.4, 129.3, 129.1, 125.1, 124.6, 57.8, 51.9, 42.1, 38.9, 26.2, 24.4, 22.9, 21.8.

Minor Isomer

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.53 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.41 (dd, *J* = 3.2, 1.3 Hz, 1H), 7.39 – 7.30 (m, 5H), 7.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.66 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.92 (dd, *J* = 15.4, 11.0 Hz, 1H), 3.81 (s, 3H), 3.66 (ddd, *J* = 15.5, 5.4, 1.8 Hz, 1H), 3.48 (ddd, *J* = 15.2, 5.4, 1.0 Hz, 1H), 2.46 (ddd, *J* = 15.2, 11.6, 1.8 Hz, 1H), 1.76 – 1.72 (m, 2H), 1.29 (ddd, *J* = 14.1, 8.5, 5.6 Hz, 1H), 0.76 (d, *J* = 3.8 Hz, 3H), 0.75 (d, *J* = 3.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.7, 144.6, 142.3, 136.2, 133.0, 132.6, 131.8, 129.7, 129.3, 129.2, 128.5, 125.2, 124.4, 59.2, 52.7, 43.1, 39.3, 28.3, 24.8, 22.4, 22.3.

(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.91)



Yield 30%;

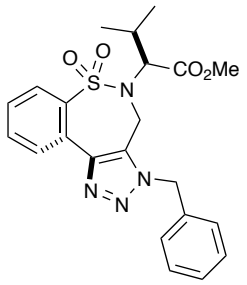
FTIR (neat): 2968, 1740, 1434, 1340, 1163, 1043, 912, 742 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 – 7.79 (m, 1H), 7.68 – 7.65 (m, 1H), 7.56 (s, 1H), 7.39 – 7.30 (m, 5H), 7.21 (dd, *J* = 7.7, 1.8 Hz, 2H), 5.70 (d, *J* = 15.6 Hz, 1H), 5.60 (d, *J* = 15.6 Hz, 1H), 4.89 (dd, *J* = 16.3, 0.8 Hz, 1H), 4.71 (d, *J* = 16.3 Hz, 1H), 4.21 (d, *J* = 10.4 Hz, 1H), 3.56 (s, 3H), 1.84 (dp, *J* = 10.4, 6.6 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.1, 139.0, 135.5, 135.3, 134.9, 133.9, 132.9, 132.1, 129.0, 128.4, 127.7, 127.3, 119.7, 65.8, 51.8, 51.7, 38.0, 29.2, 19.8, 19.3;

HRMS calculated for $C_{22}H_{25}BrN_4O_4SNa$ $(M+Na)^+$ 543.0678, found 543.0680.

(*S*)-Methyl 2-(3-benzyl-6,6-dioxido-3*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.92)



Yield 13%;

Mp 140 ºC;

$[\alpha]_D^{25} = -1.94$ (*c* = 0.52, CH_2Cl_2);

FTIR (neat): 2966, 1378, 1434, 1342, 1161, 1045, 706 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.65 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67 (td, *J* = 8.0, 1.4 Hz, 1H), 7.49 – 7.31 (m, 4H), 7.26 – 7.21 (m, 2H), 5.61 (d, *J* = 15.9 Hz, 1H), 5.53 (d, *J* = 15.8 Hz, 1H), 4.73 (d, *J* = 17.3 Hz, 1H), 4.53 (d, *J* = 17.4 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.01 (s, 3H), 1.87 – 1.77 (m, 1H), 0.97 – 0.88 (m, 3H), 0.79 (d, *J* = 6.5 Hz, 3H);

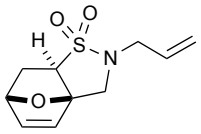
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.9, 141.7, 137.9, 133.3, 133.1, 133.0, 129.3, 128.8, 128.6, 128.0, 127.9, 127.5, 127.2, 64.3, 52.7, 51.6, 39.9, 28.6, 18.9, 18.8;

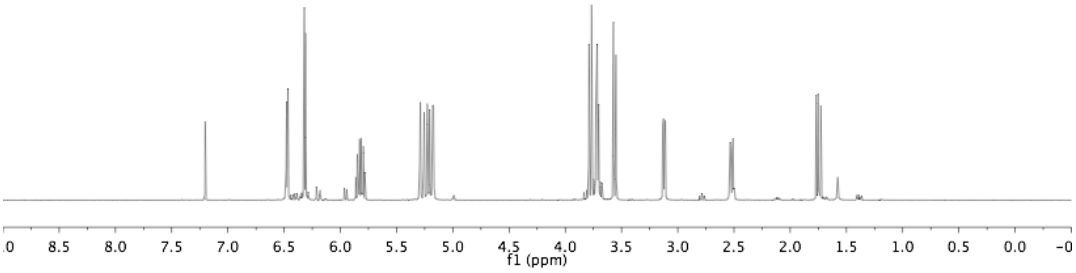
HRMS calculated for $C_{22}H_{24}N_4O_4SNa$ $(M+Na)^+$ 463.1416, found 463.1420.

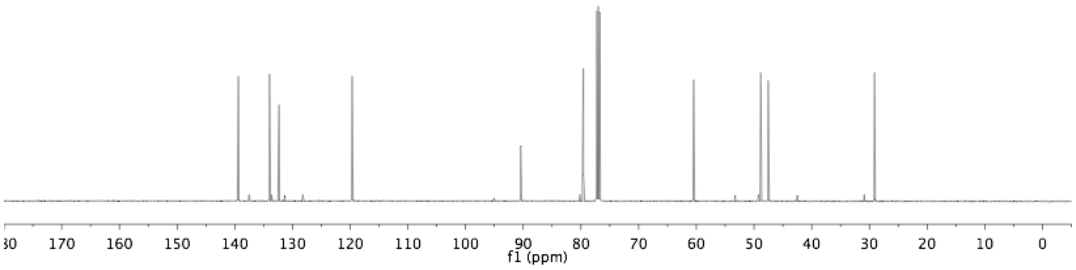
Appendix

NMR Spectra and X-Ray Data

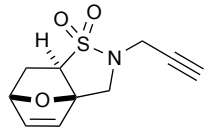
6*H*-3a,6-Epoxy-1,2-Benzisothiazole, 2,3,7,7a-tetrahydro-2-allyl 1,1-dioxide [(±)-2.23]

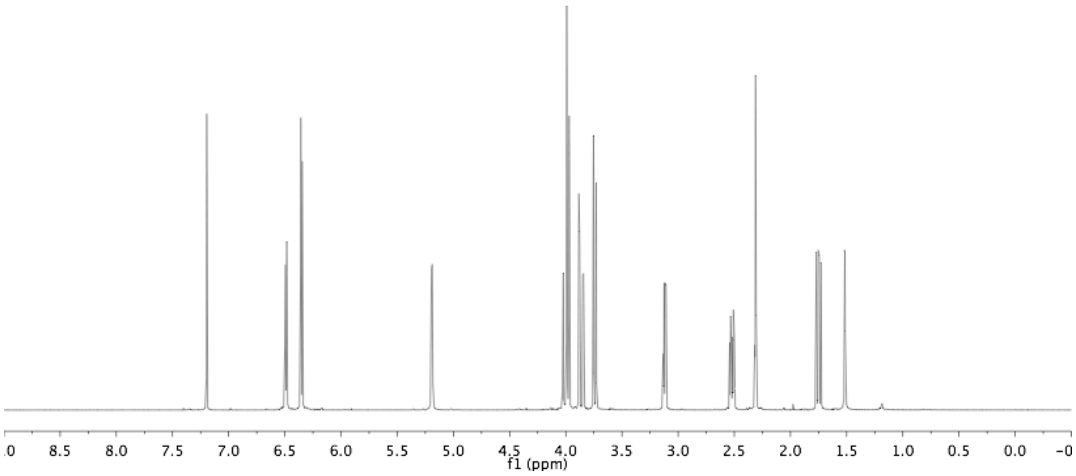


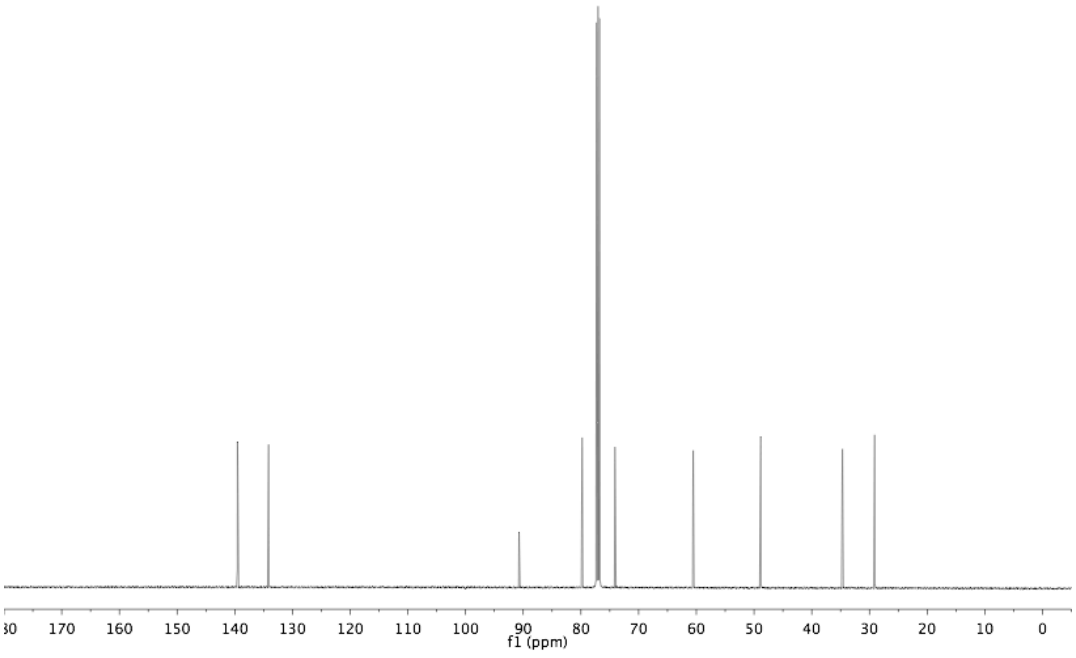




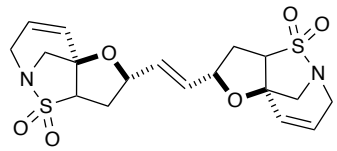
6*H*-3a,6-Epoxy-1,2-Benzisothiazole, 2,3,7,7a-tetrahydro-2-propargyl, 1,1-dioxide [(±)2.24]

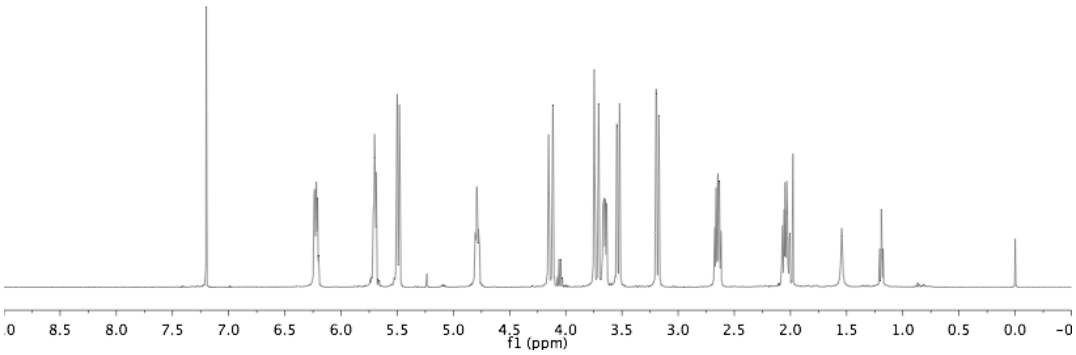


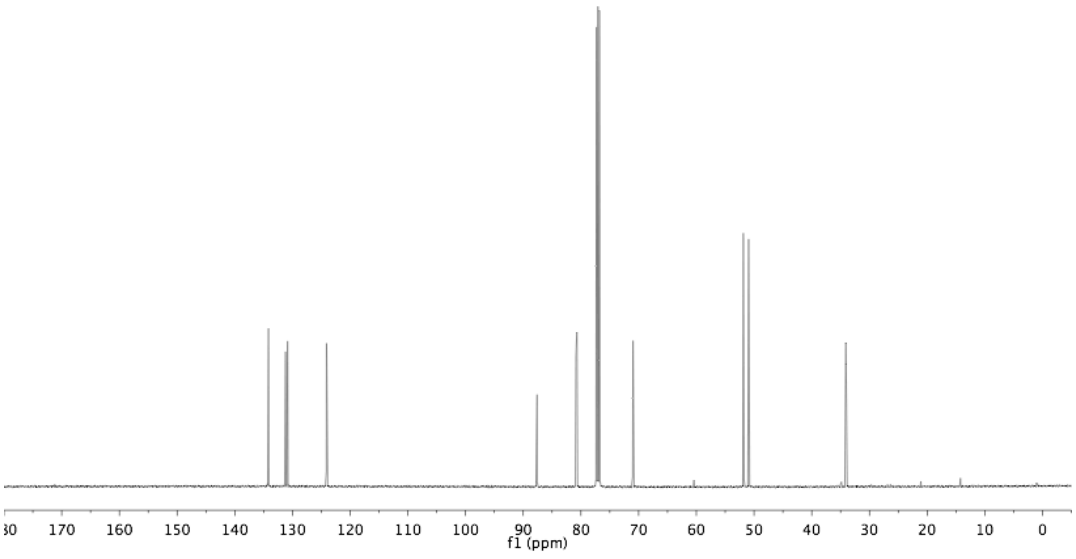




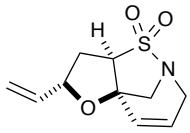
(5a*R*,5a'*R*)-7,7'-((*E*)-Ethene-1,2-diyl)bis(3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide) [(±)-2.25]

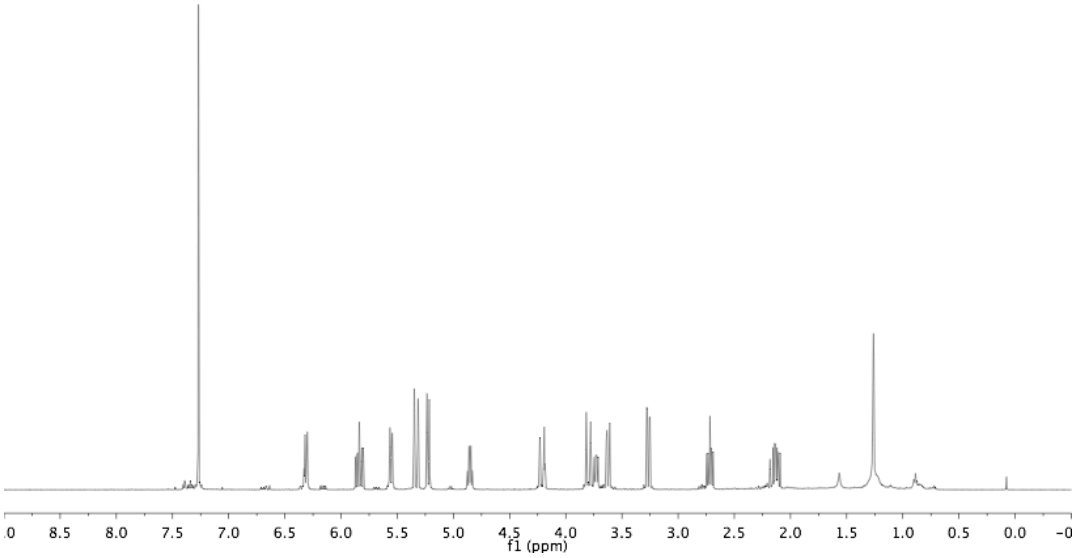


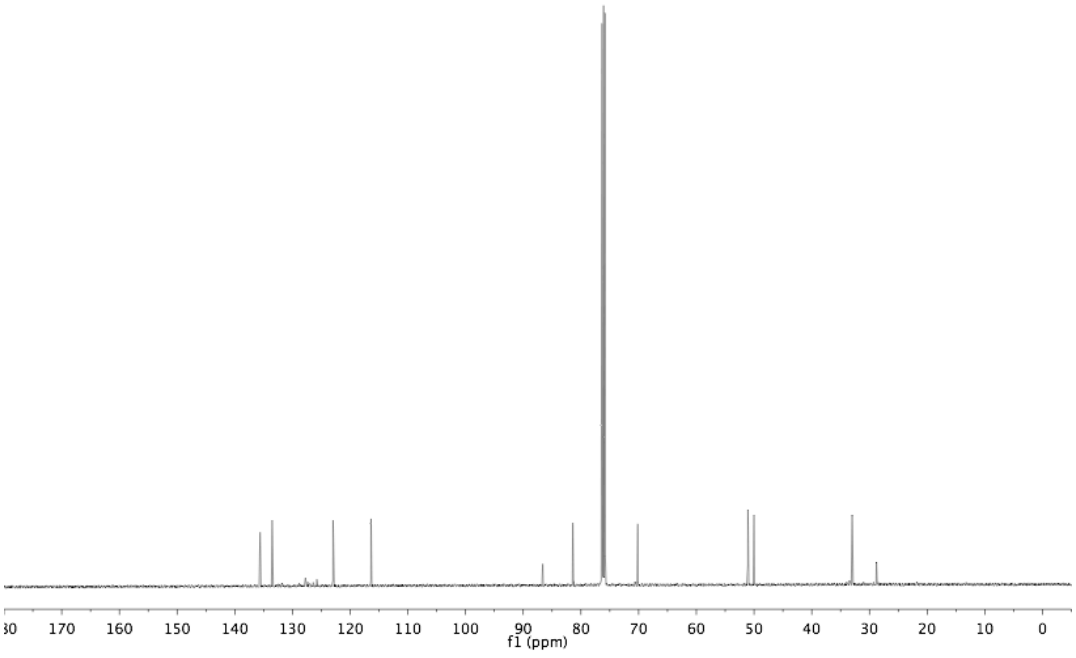




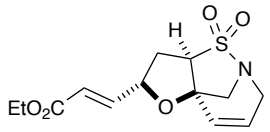
(5a*R*,8a*R*)-7-Vinyl-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.26]

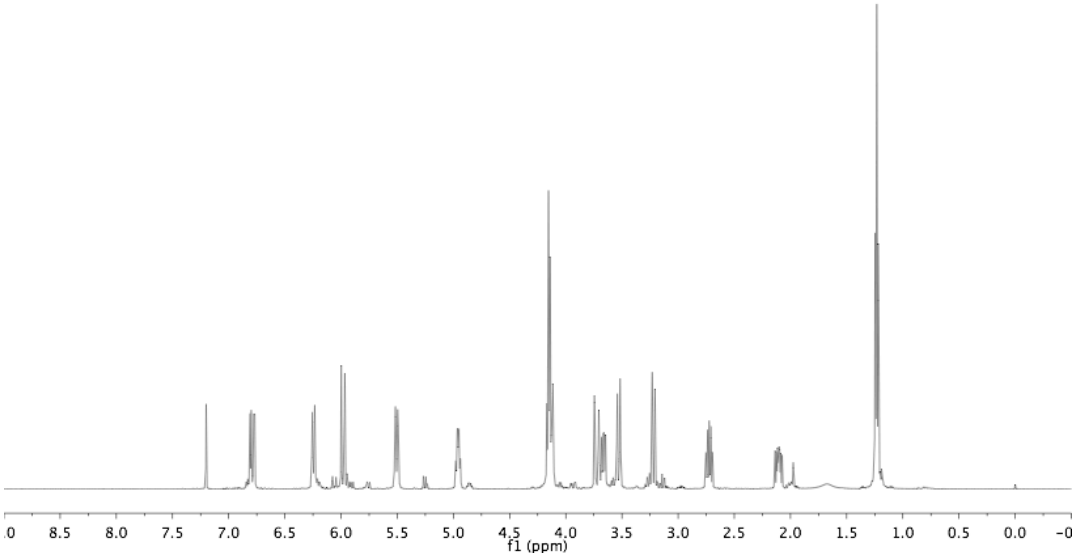


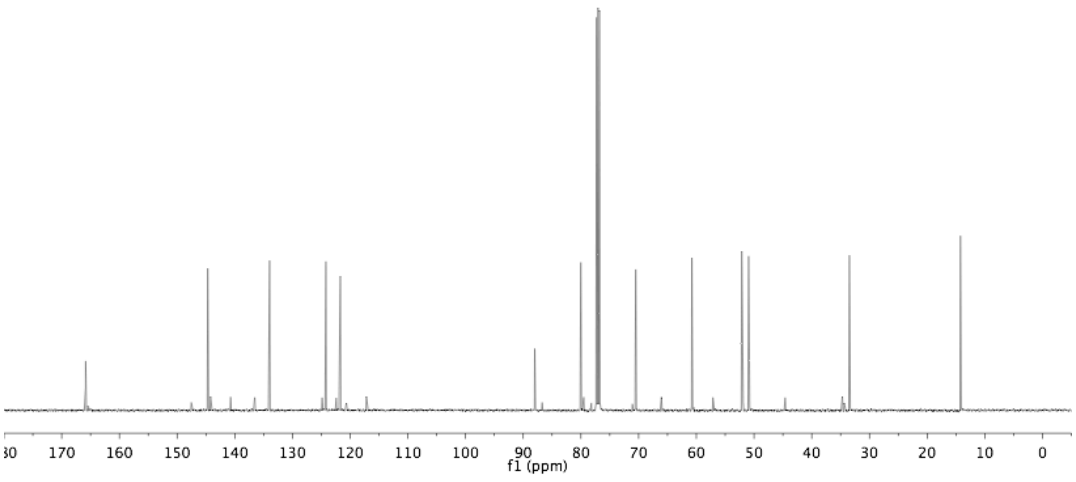




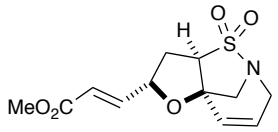
(*E*)-Ethyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.27]

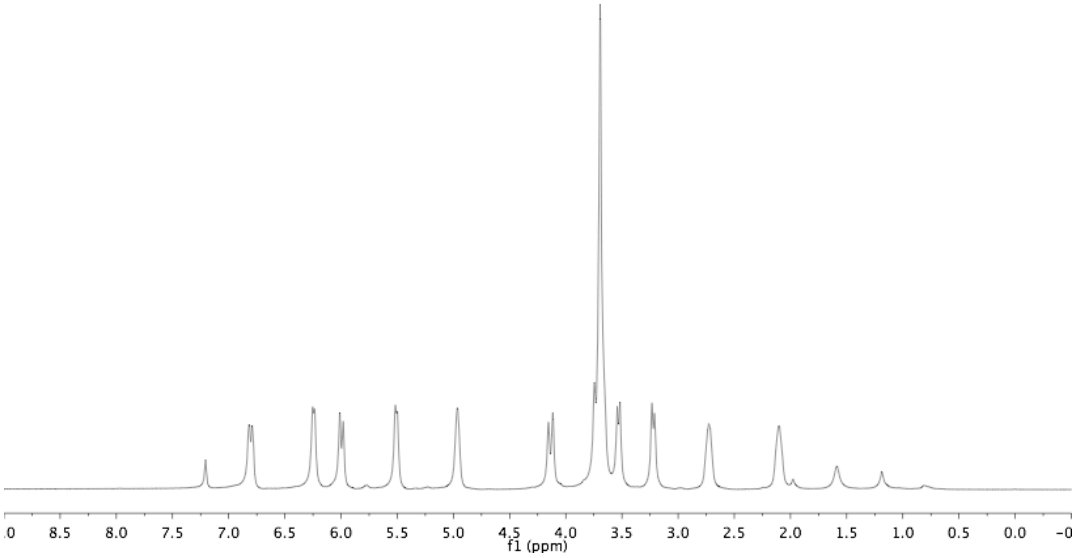


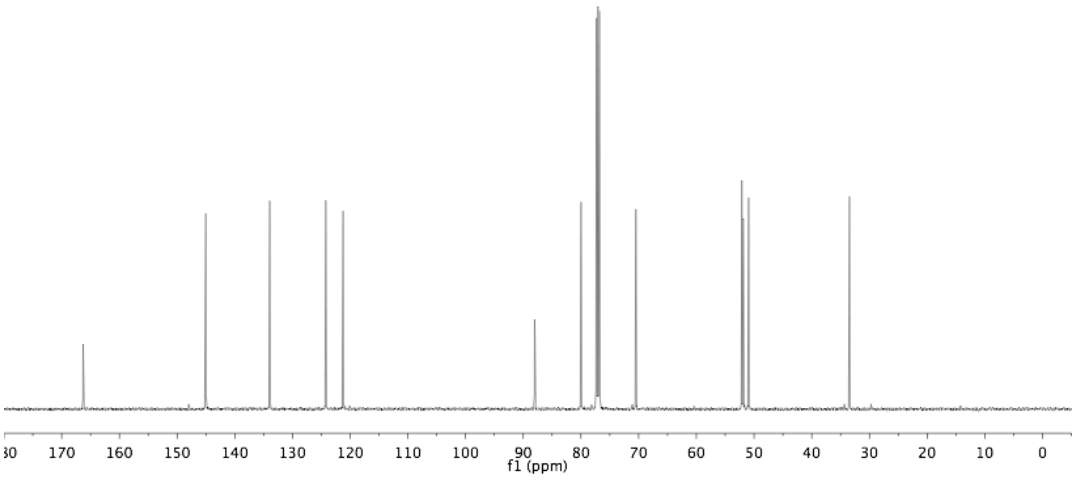




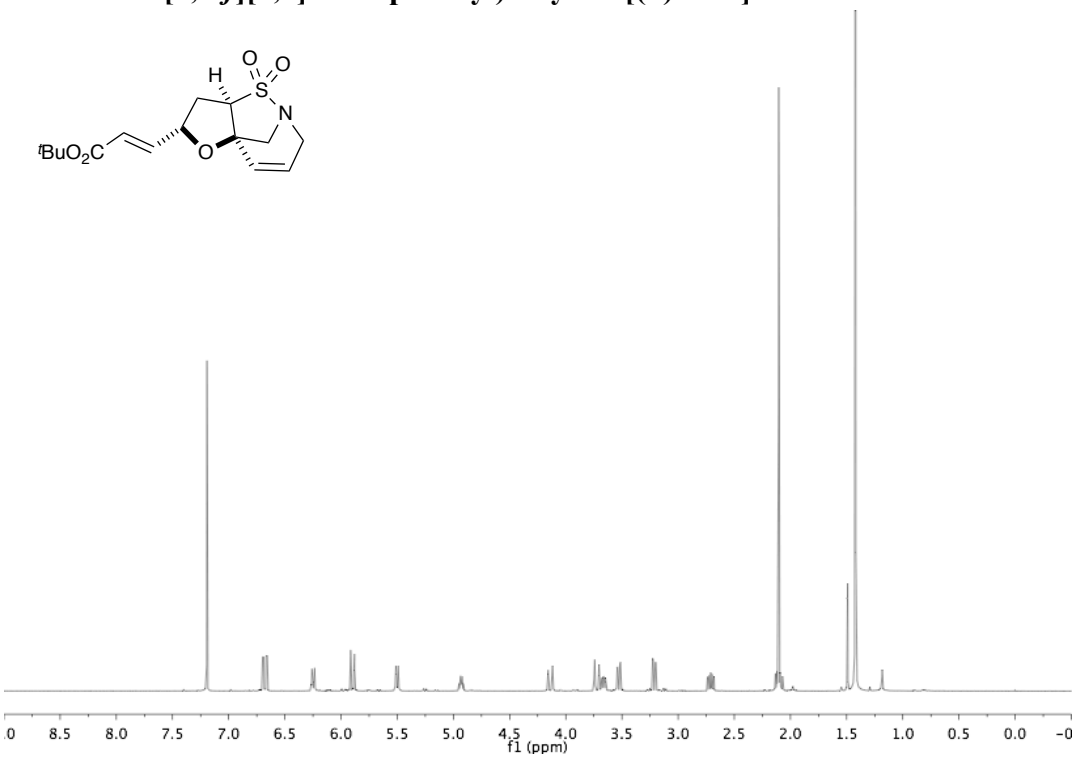
(*E*)-Methyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.28]

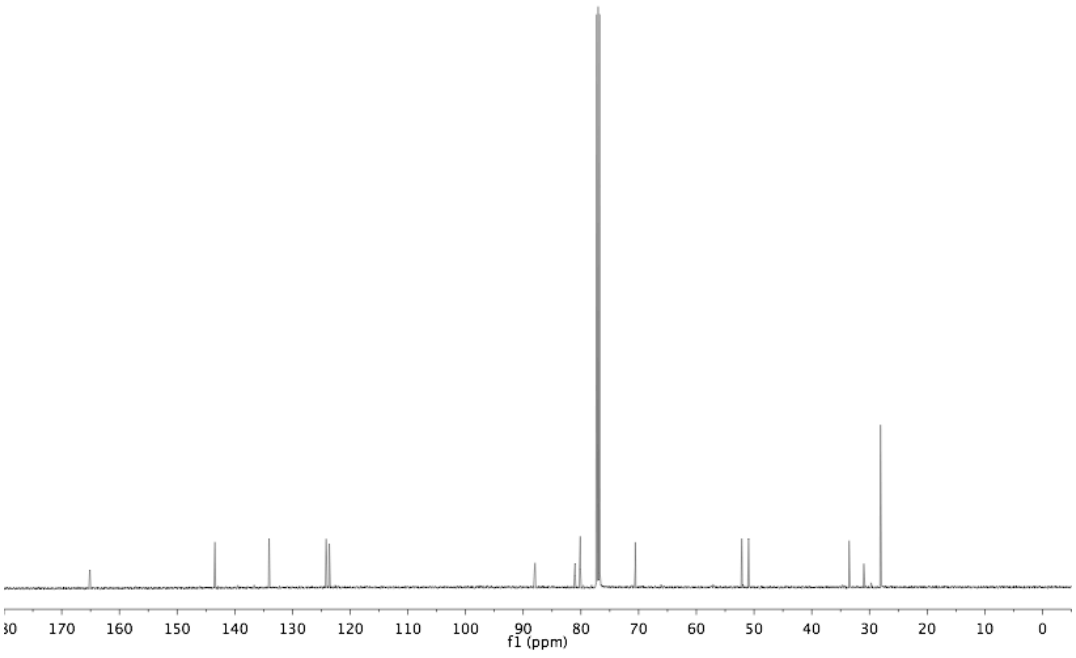




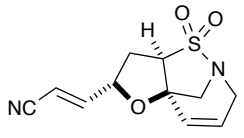


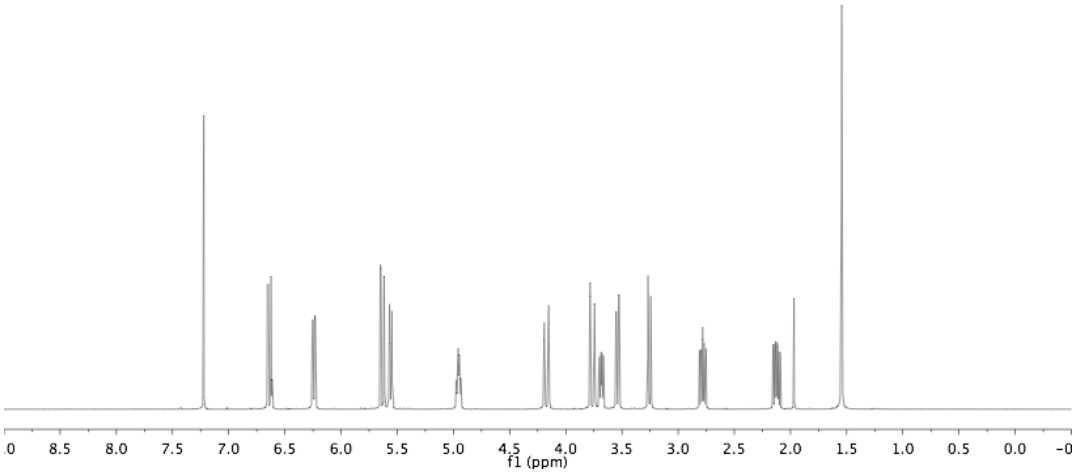
(*E*)-*tert*-Butyl 3-((5a*R*,8a*R*)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylate [(±)-2.29]

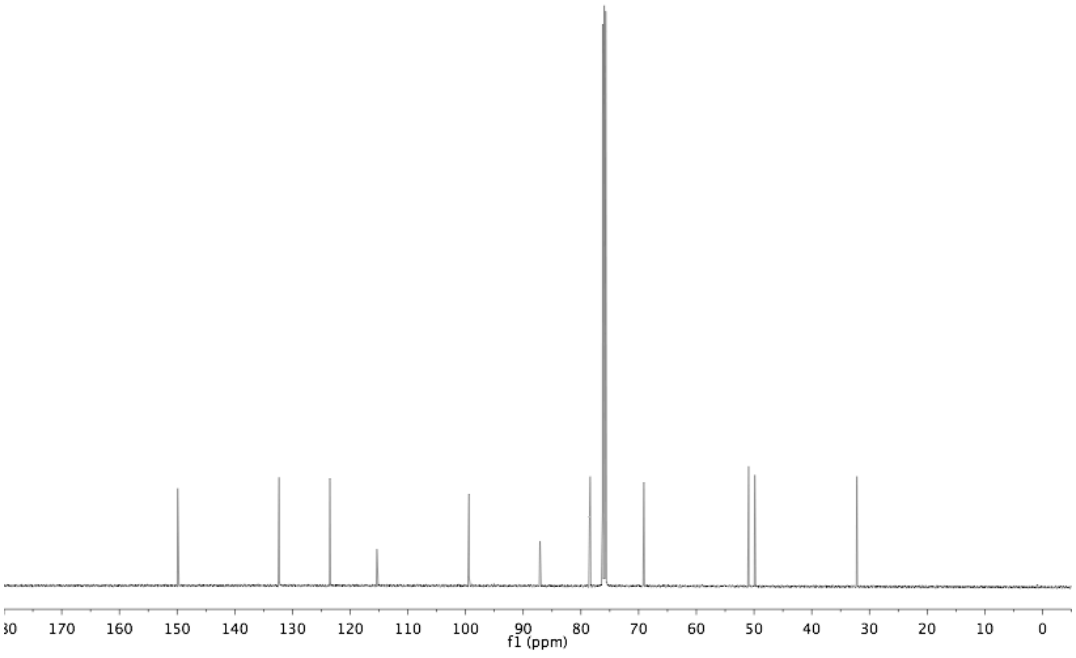




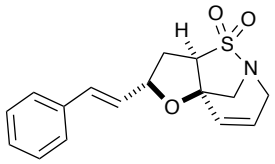
(*E*)-3-((5a*R*,8a*R*)-1,1-Dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepin-7-yl)acrylonitrile [(±)-2.30]

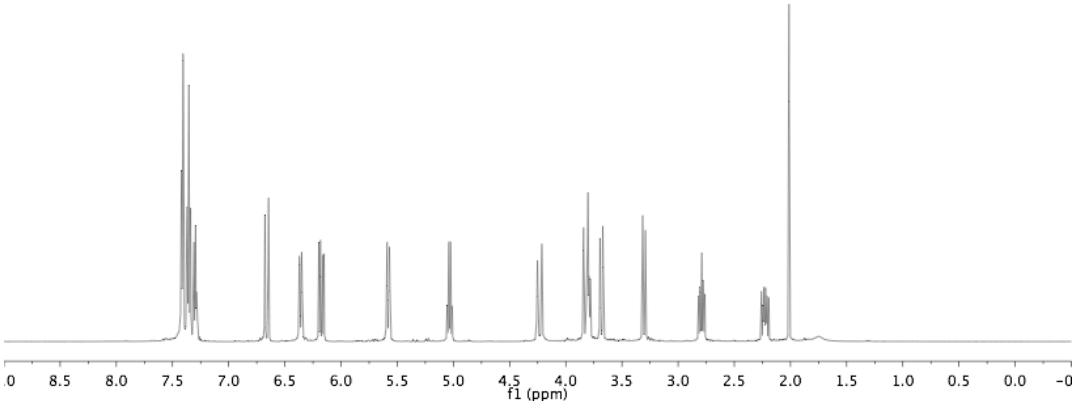


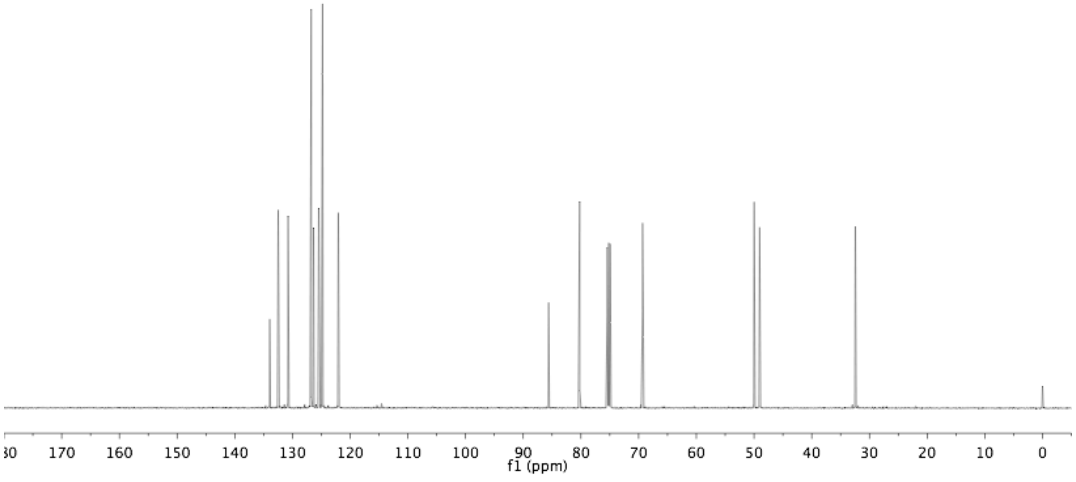




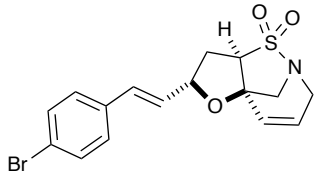
(5a*R*,8a*R*)-7-((*E*)-Styryl)-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.31]

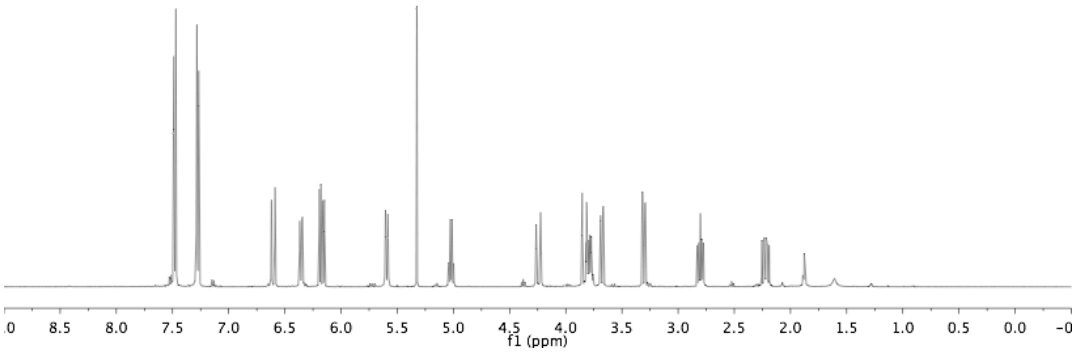


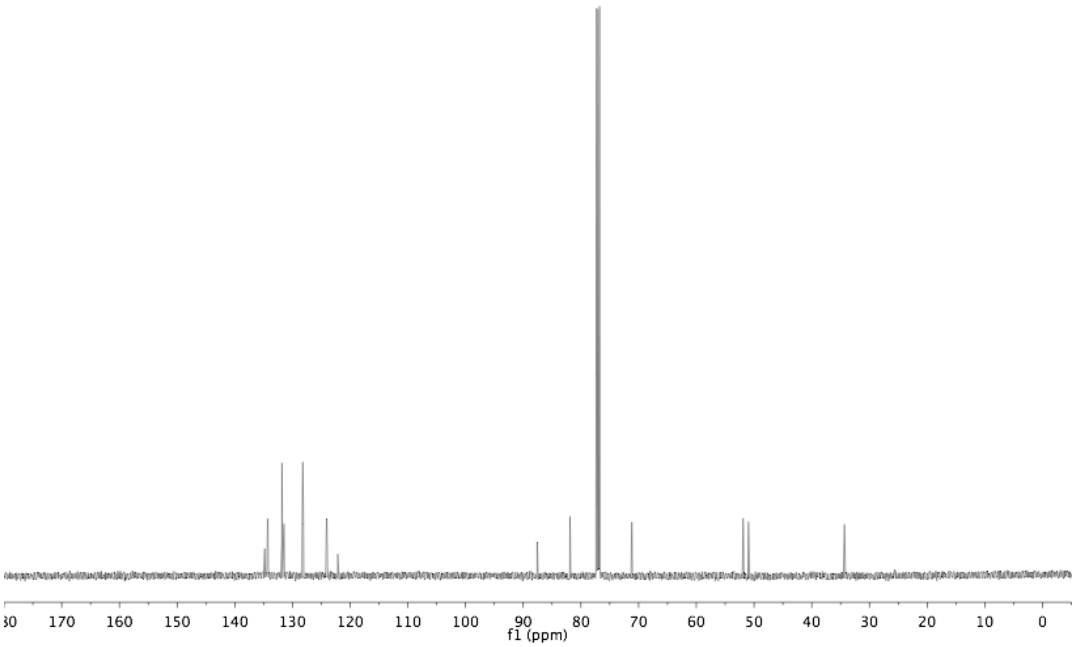




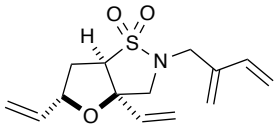
(5a*R*,8a*R*)-7-((*E*)-4-Bromostyryl)-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine 1,1-dioxide [(±)-2.32]

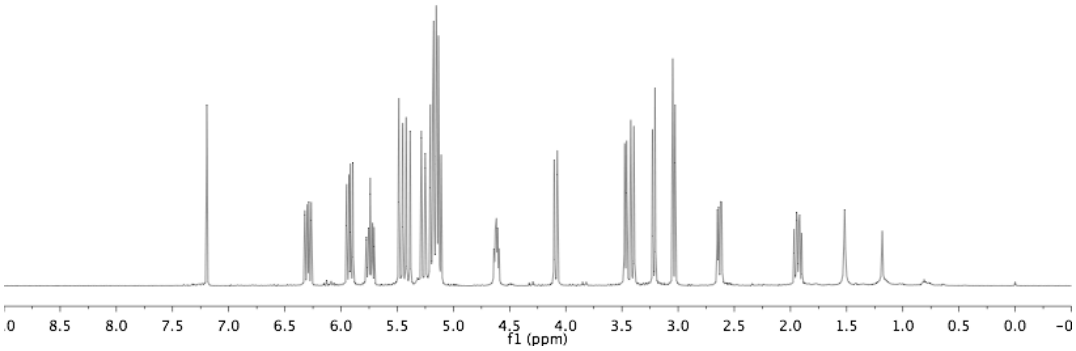


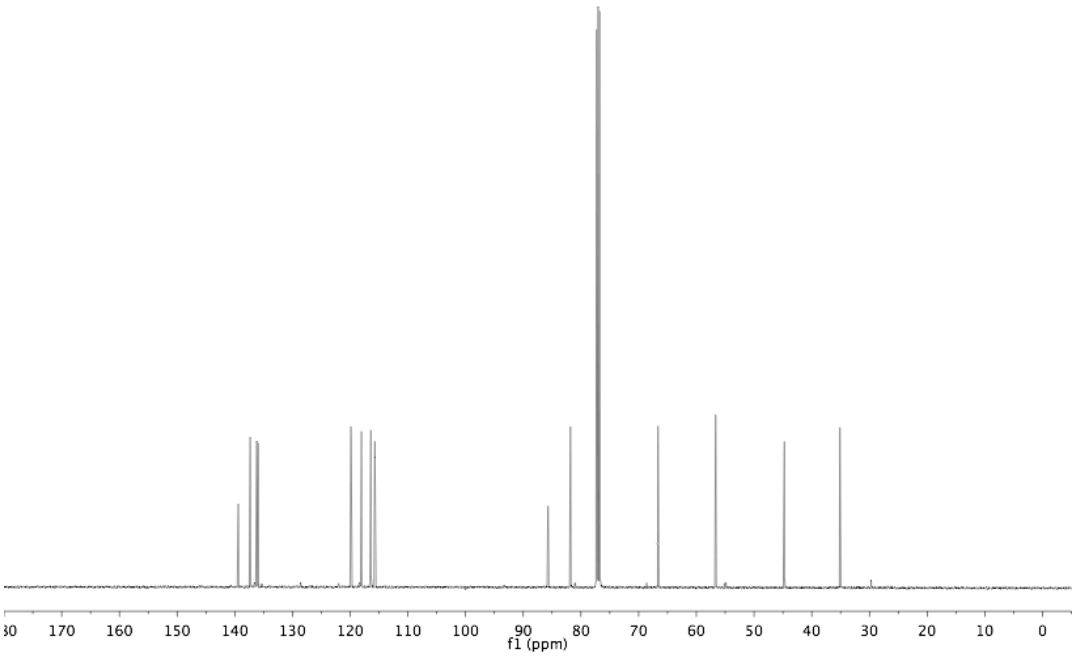




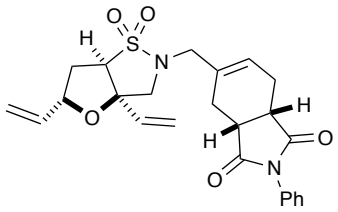
(3a*R*,6a*R*)-2-(2-Methylenebut-3-en-1-yl)-3a,5-divinylhexahydrofuro[2,3-*d*]isothiazole 1,1-dioxide [(±)-2.34]

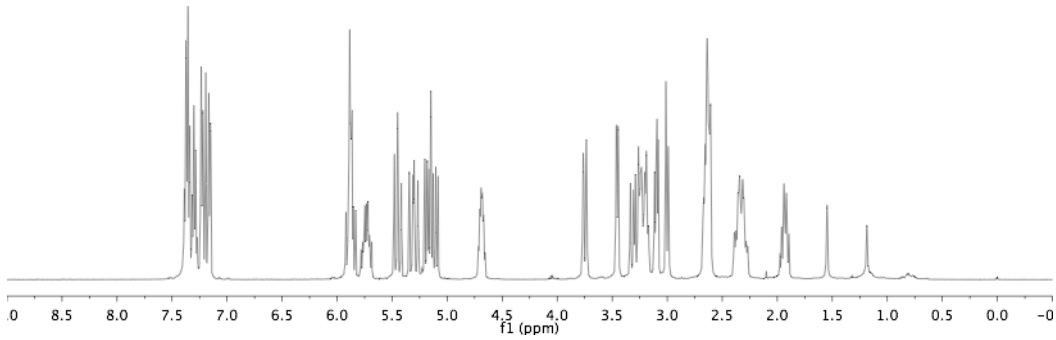


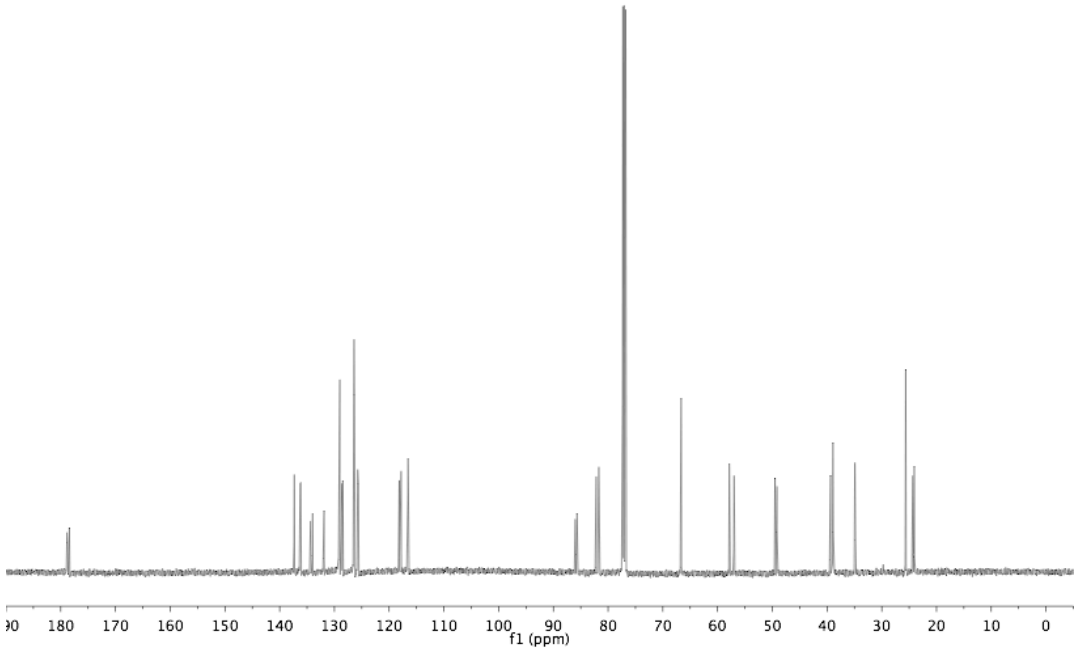




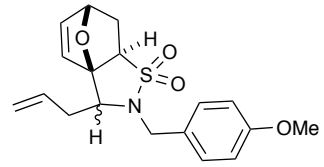
(3a*R*,7a*S*)-5-(((3a*R*,6a*R*)-1,1-Dioxido-3a,5-divinyltetrahydrofuro[2,3-*d*]isothiazol-2(5*H*)-yl)methyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [(±)-2.35]

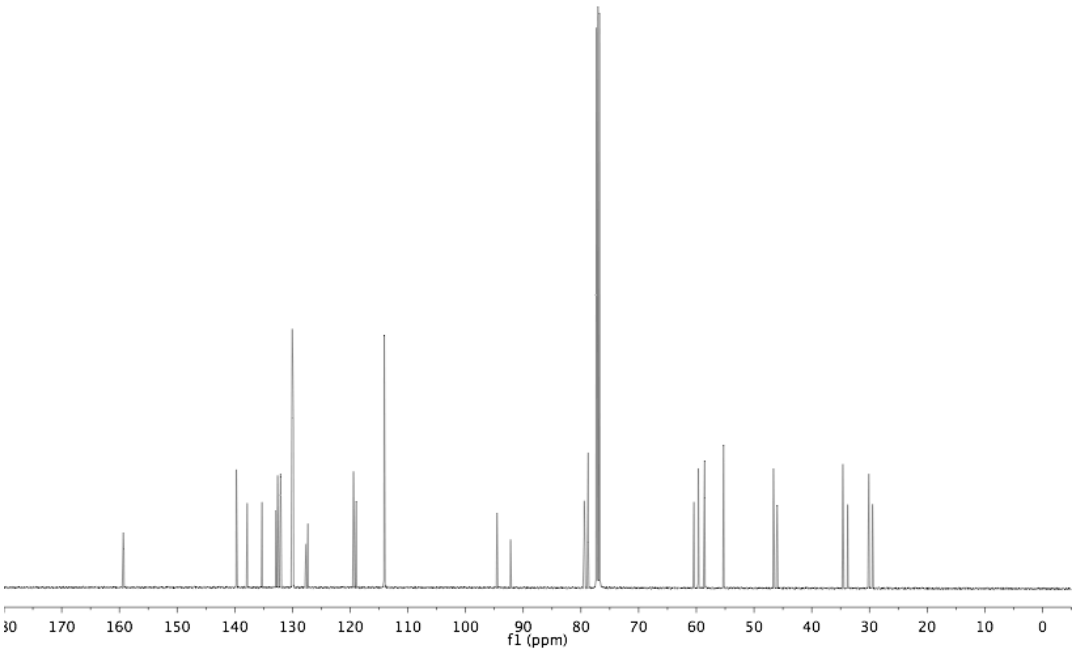




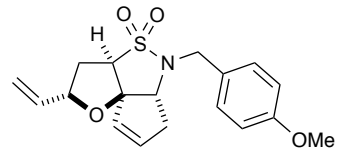


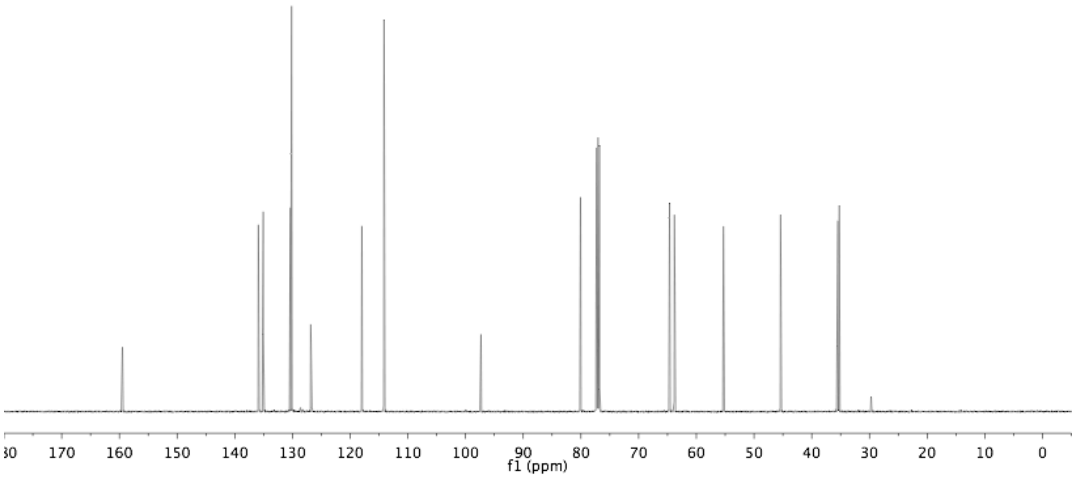
(3a*R*,6*S*,7a*R*)-3-Allyl-2-(4-methoxybenzyl)-3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole 1,1-dioxide [(±)-2.37]

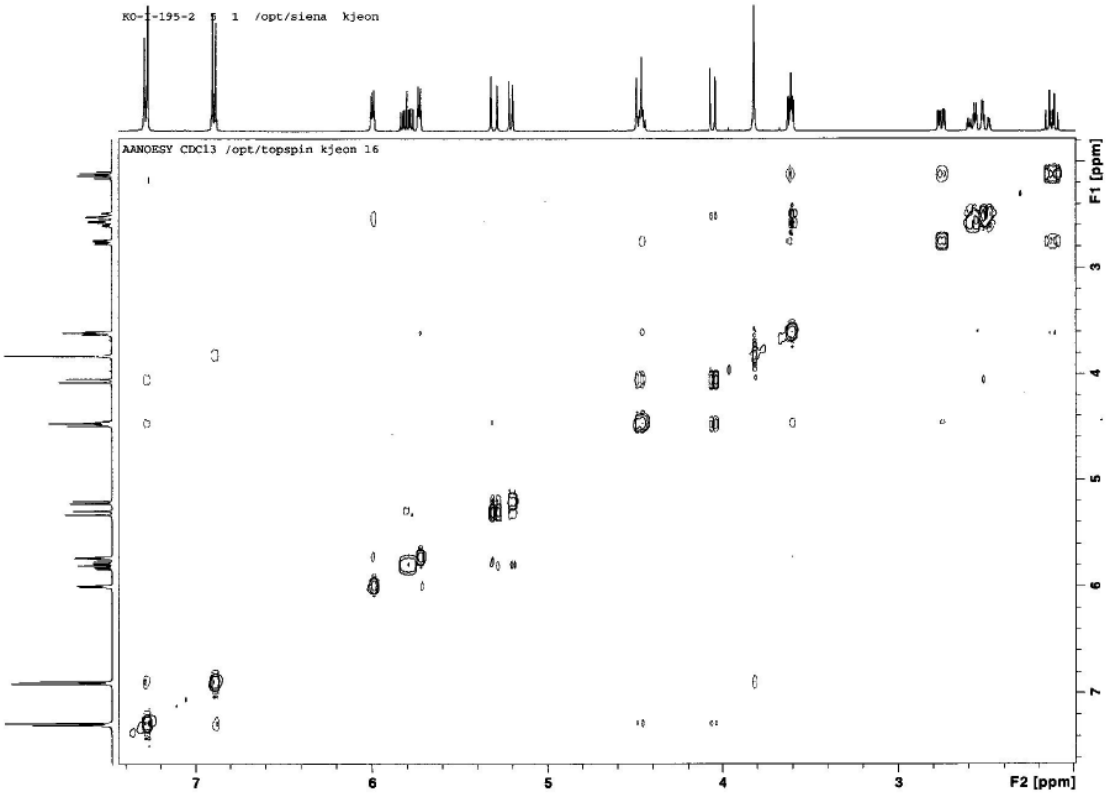




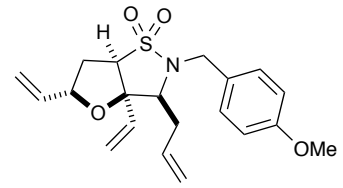
(2*S*,3a*R*,5a*R*,8a*R*)-5-(4-Methoxybenzyl)-2-vinyl-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazole 4,4-dioxide [(±)-2.38]

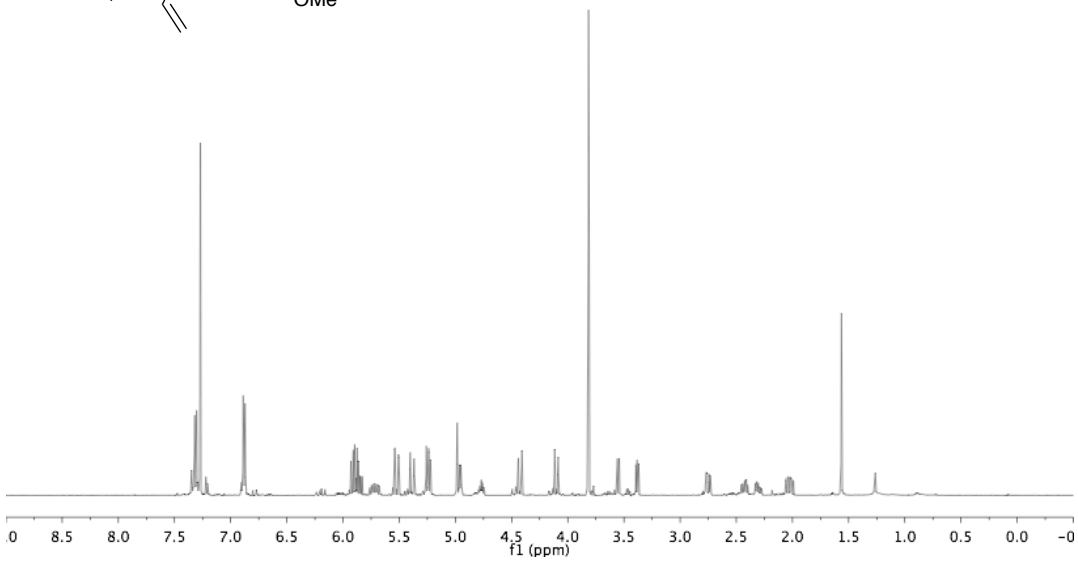


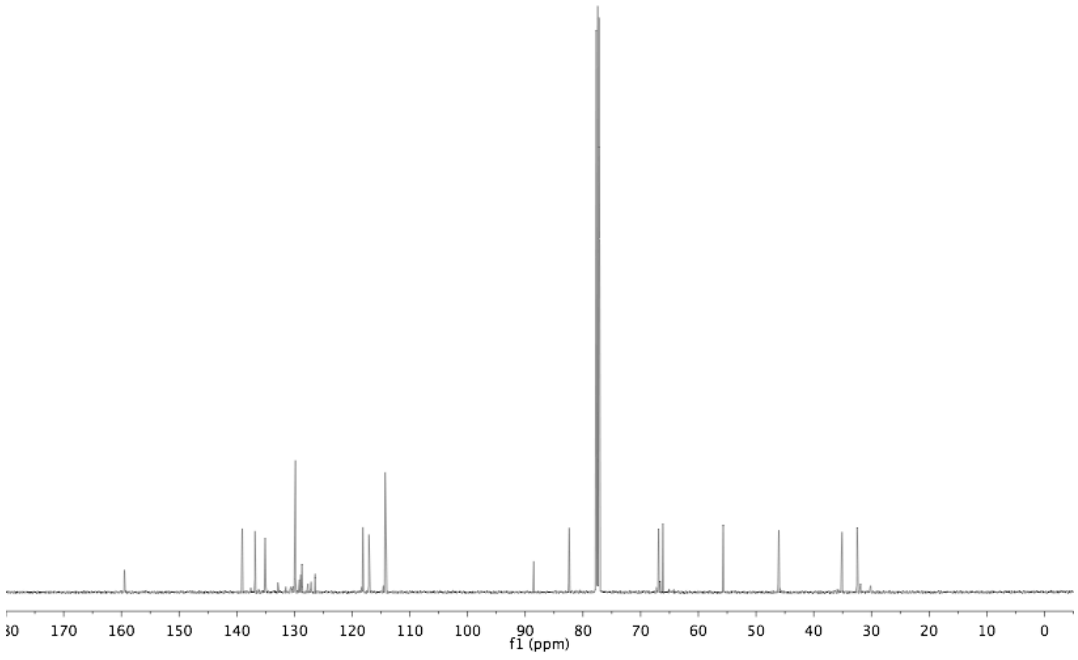


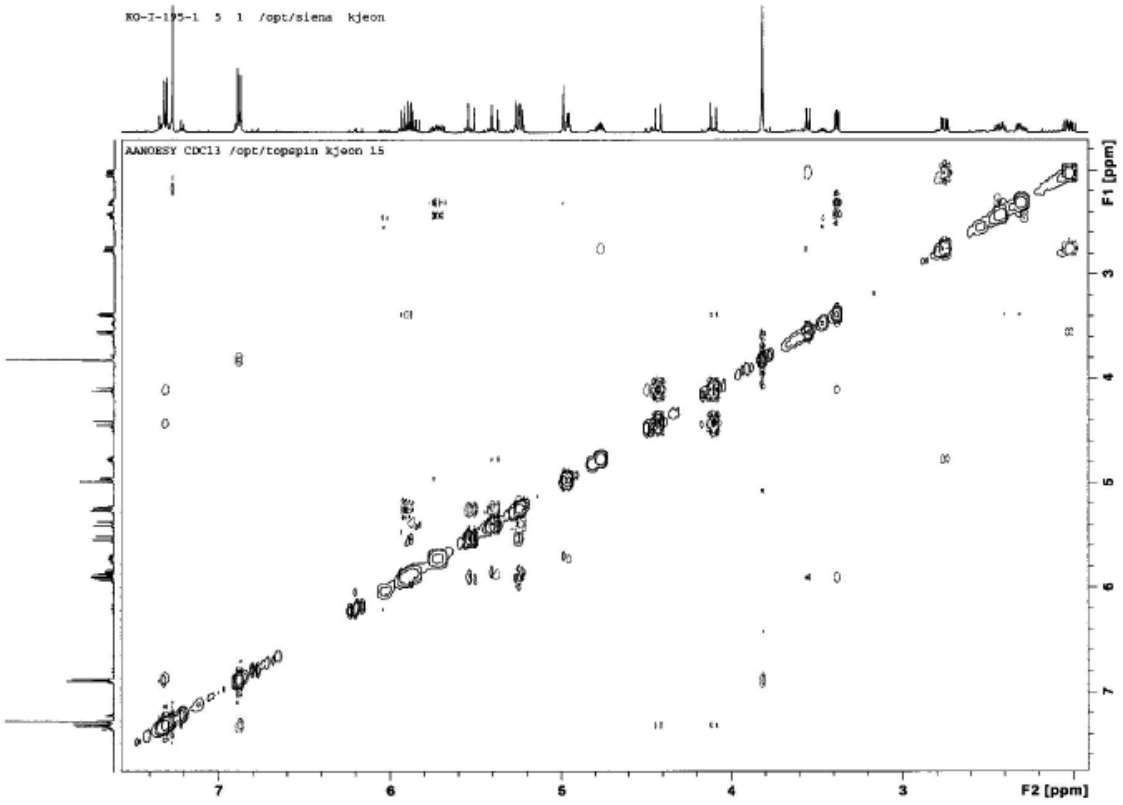

AANOESY CDCl3 /opt/topspin kjeon 16
F1 [ppm]
F2 [ppm]
7
6
5
4
3

(3*S*,3a*R*,5*S*,6a*R*)-3-Allyl-2-(4-methoxybenzyl)-3a,5-divinylhexahydrofuro[2,3-*d*]isothiazole 1,1-dioxide [(±)-2.39]

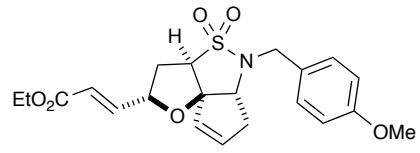


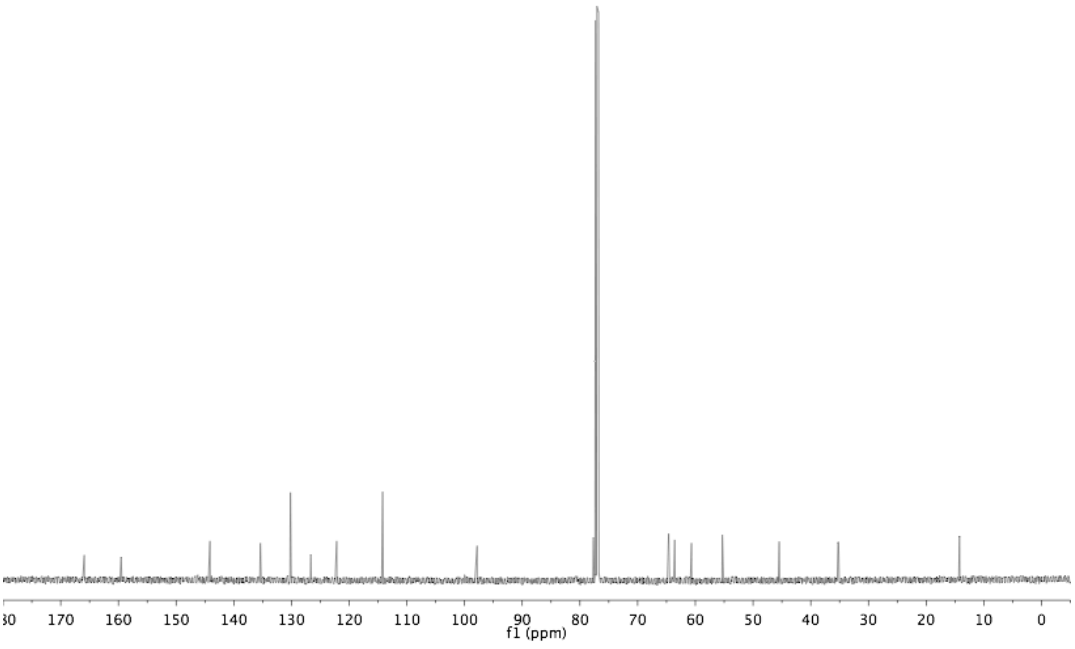




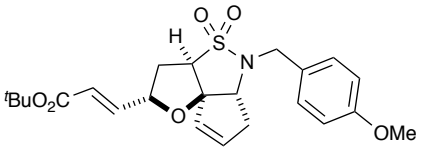

KG-I-195-1 5 1 /opt/siena kjeon
AANOESY CDCl3 /opt/topspin kjeon 15
F1 [ppm]
F2 [ppm]
7
6
5
4
3

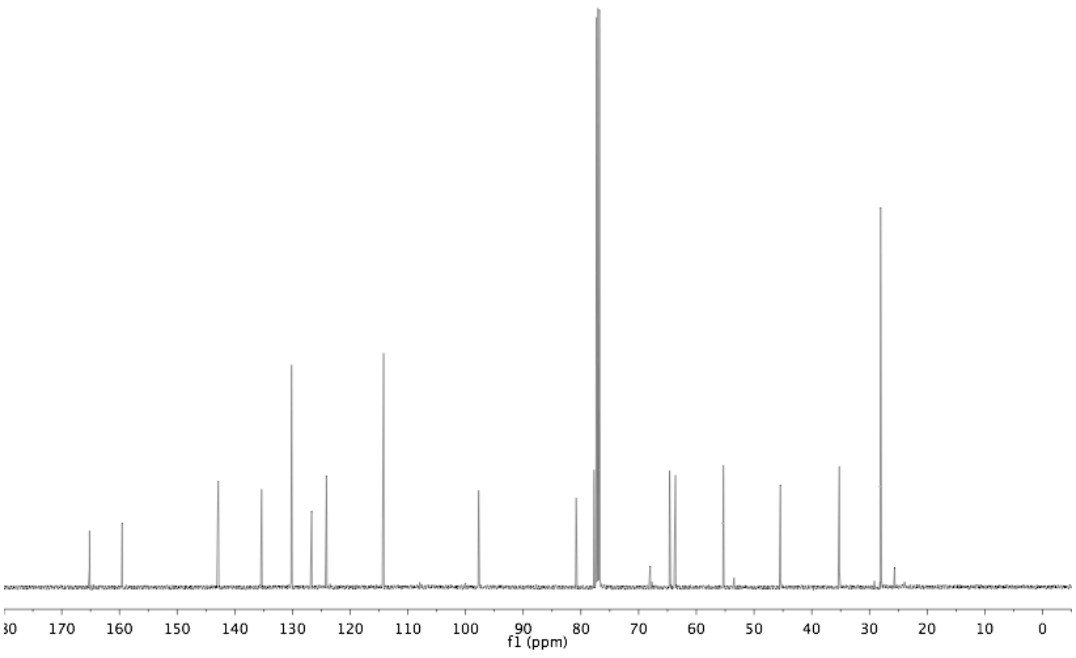
(*E*)-Ethyl 3-((2*S*,3a*R*,5a*R*,8a*R*)-5-(4-Methoxybenzyl)-4,4-dioxido-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazol-2-yl)acrylate [(±)-2.40]



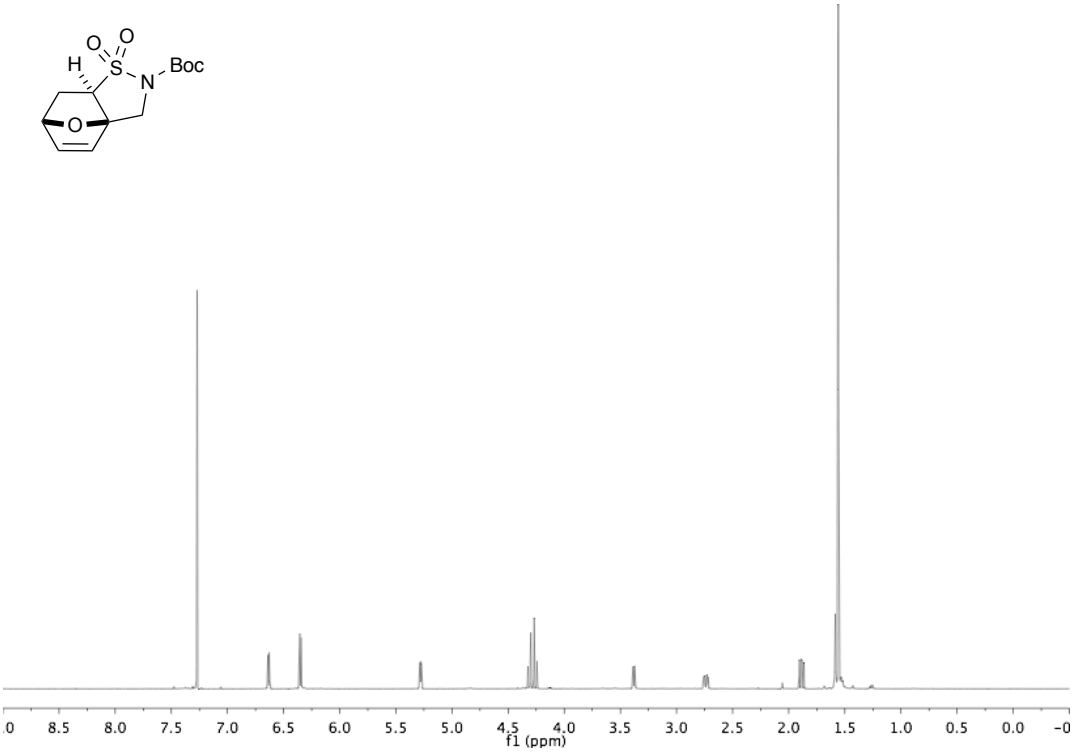


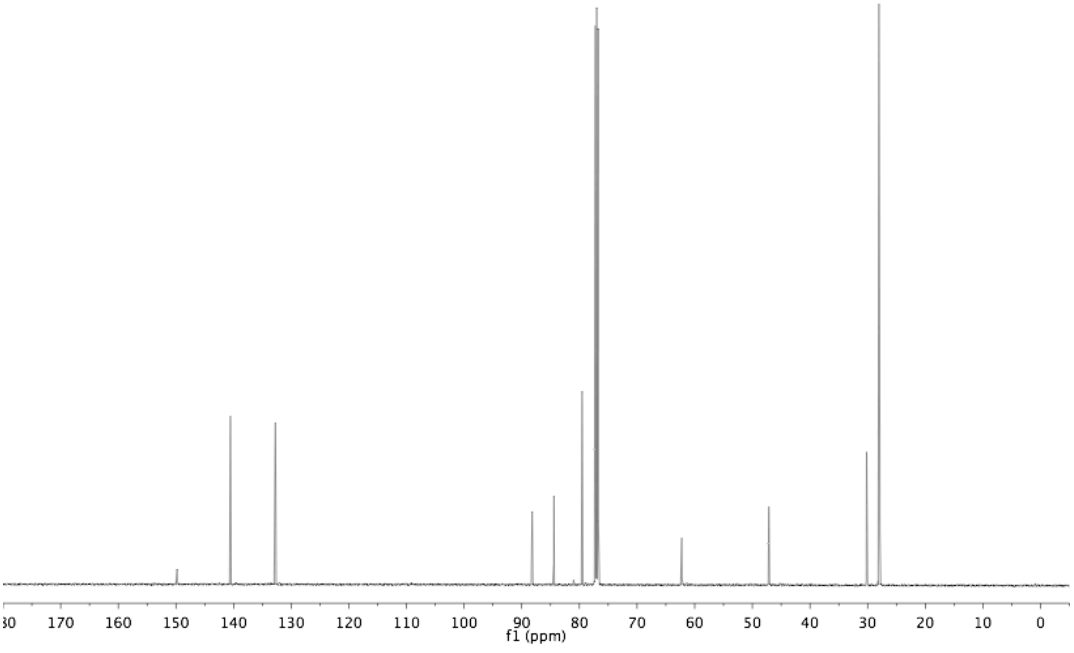
(*E*)-*tert*-Butyl 3-((2*S*,3a*R*,5a*R*,8a*R*)-5-(4-methoxybenzyl)-4,4-dioxido-2,3,3a,5,5a,6-hexahydrocyclopenta[*c*]furo[2,3-*d*]isothiazol-2-yl)acrylate [(±)-2.41]



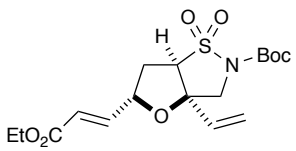


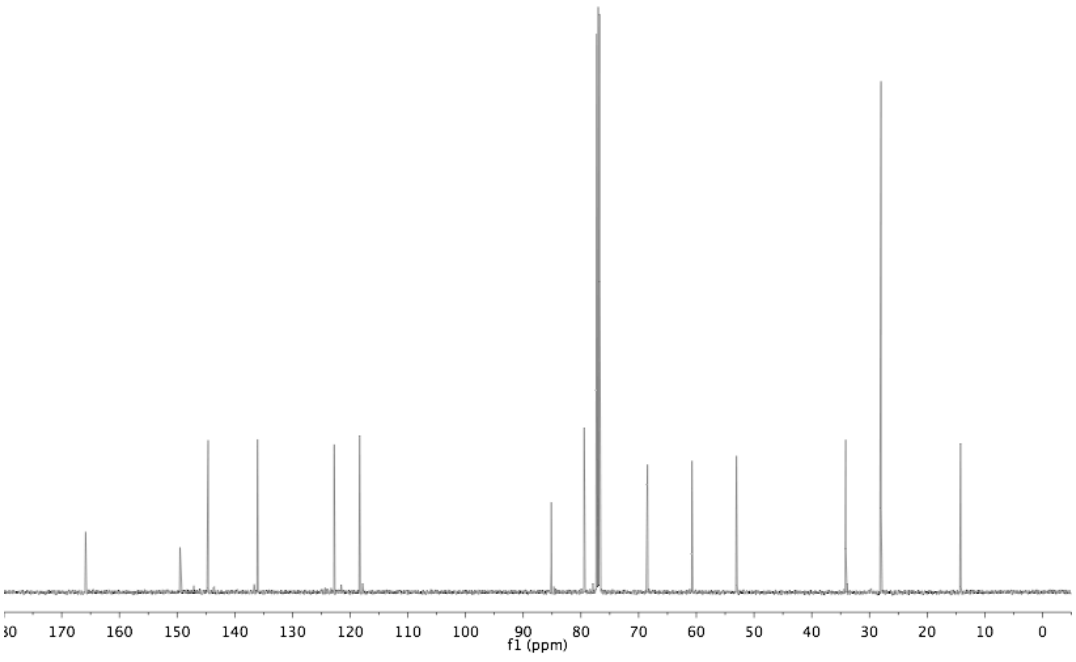
(3a*R*,6*S*,7a*R*)-*tert*-Butyl 3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole-2-carboxylate 1,1-dioxide [(±)-2.42]



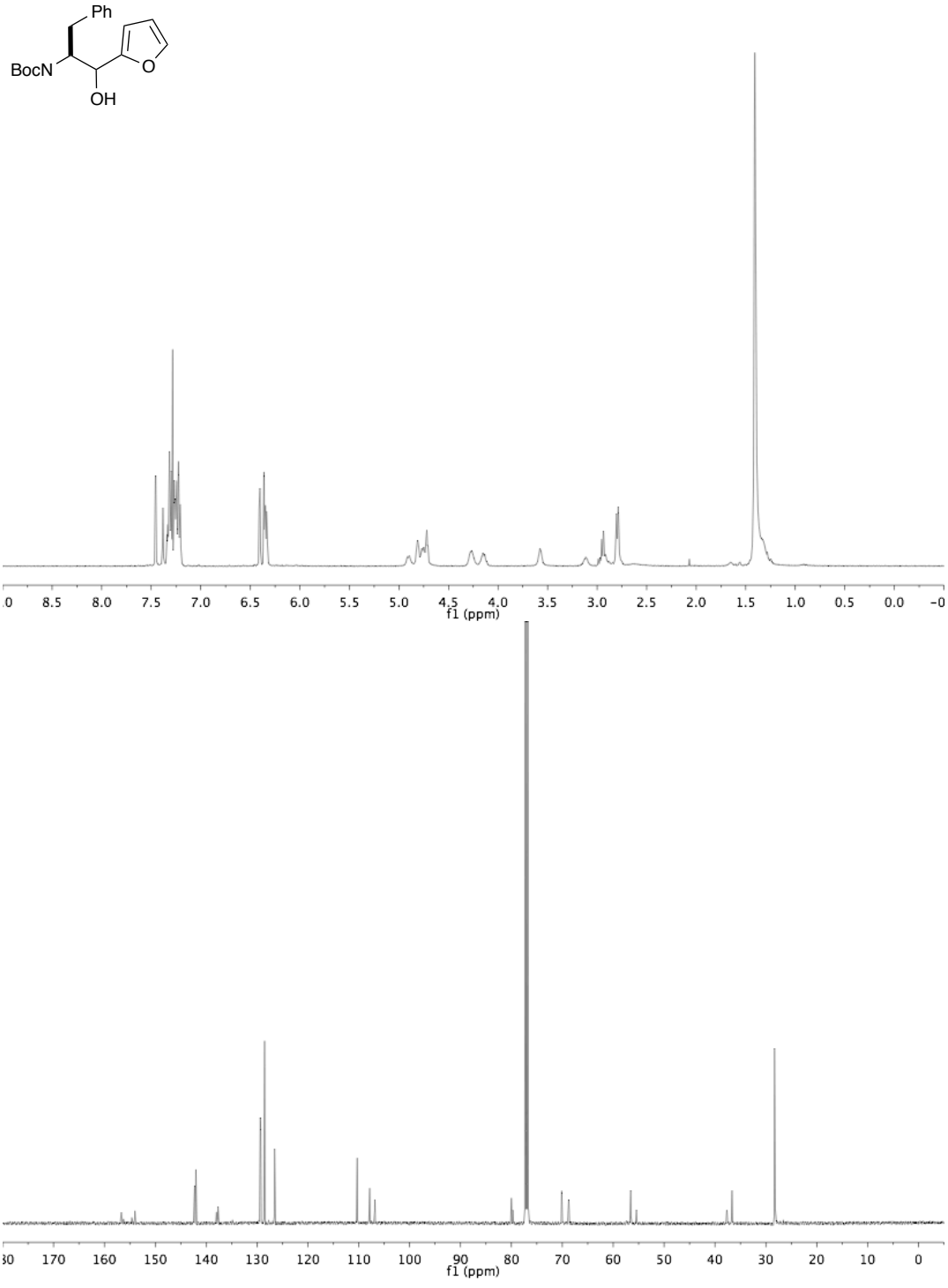


(3a*R*,6a*R*)-*tert*-Butyl 5-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-3a-vinyltetrahydrofuro[2,3-d]isothiazole-2(5*H*)-carboxylate 1,1-dioxide [(±)-2.43]

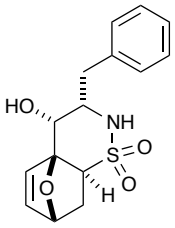


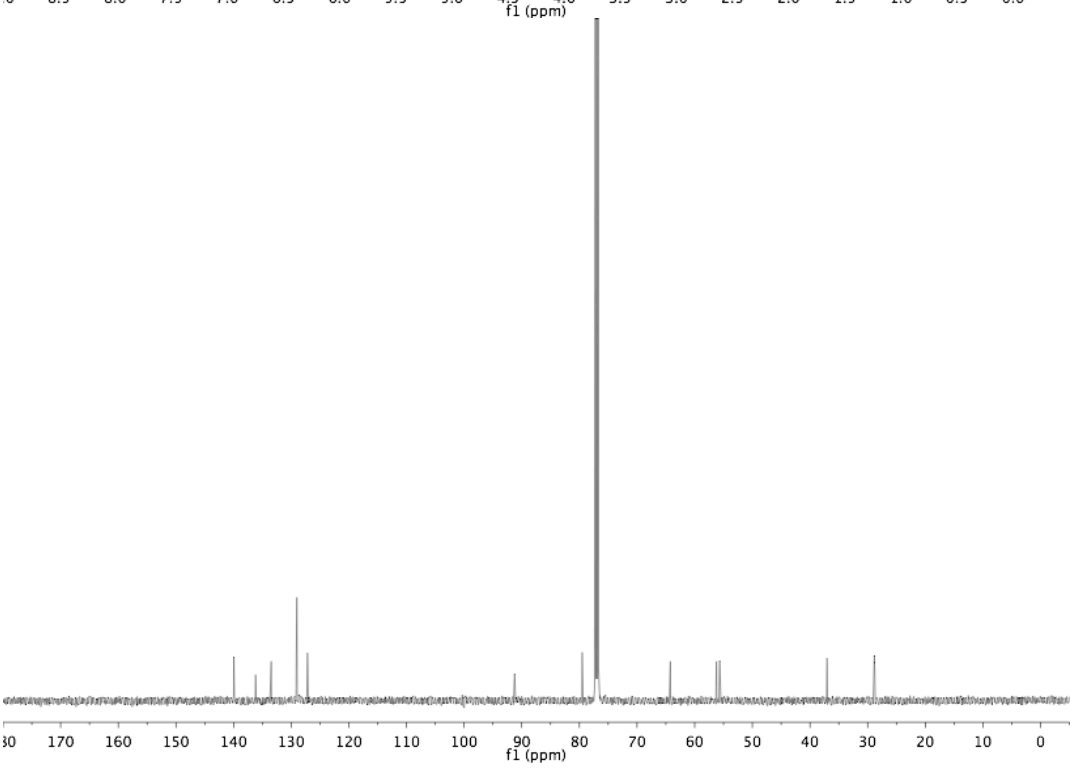


tert-Butyl (2_S_)-1-(furan-2-yl)-1-hydroxy-3-phenylpropan-2-ylcarbamate (2.45)

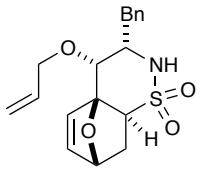


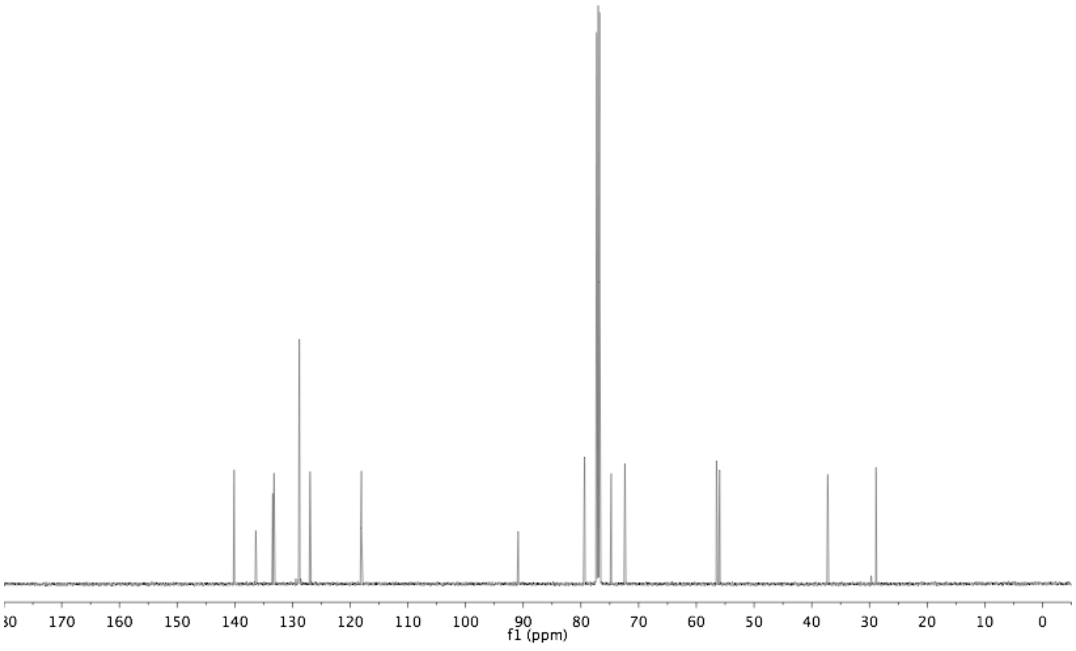
(3*S*,4*R*,4a*S*,7*R*,8a*S*)-3-Benzyl-4-hydroxy-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazine 1,1-dioxide (2.47)



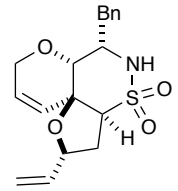


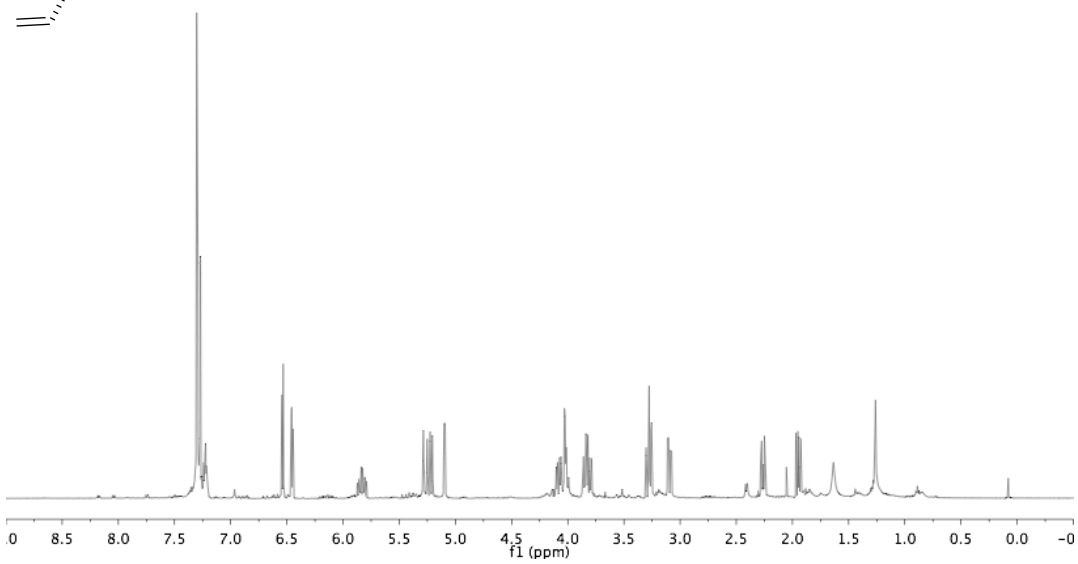
(3*S*,4*R*,4a*S*,7*R*,8a*S*)-4-(Allyloxy)-3-benzyl-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazine 1,1-dioxide (2.48)

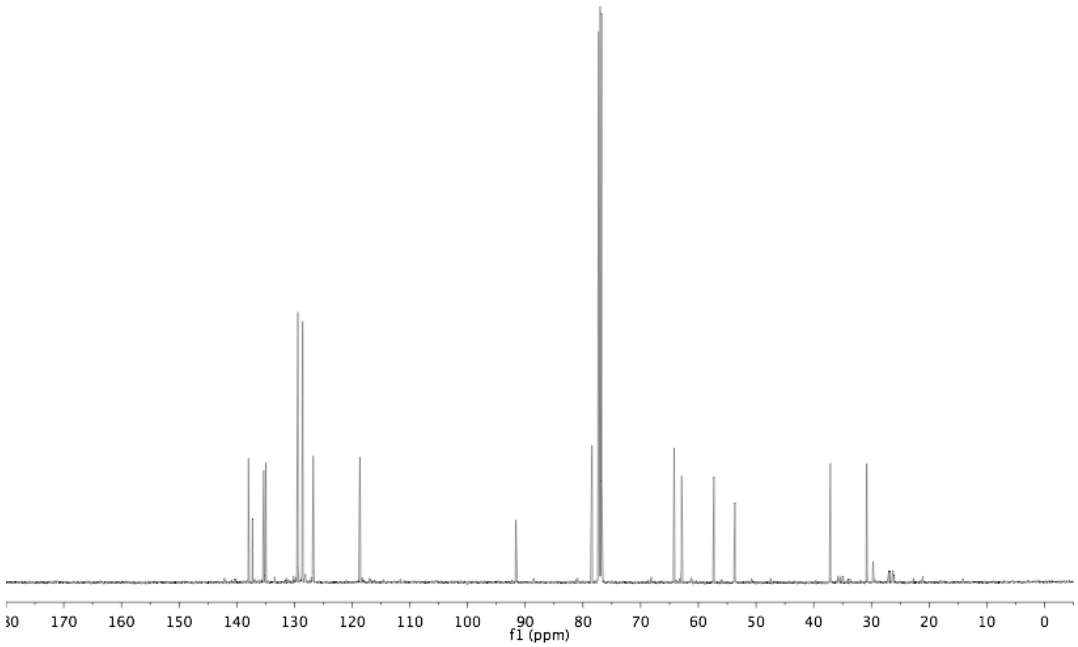




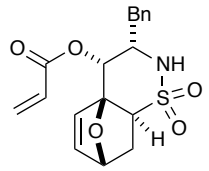
(3a*S*,6*S*,6a*R*,10a*S*)-6-Benzyl-2-vinyl-3,3a,5,6,6a,8-hexahydro-2*H*-furo[2,3-*e*]pyrano[2,3-*d*][1,2]thiazine 4,4-dioxide (2.49)

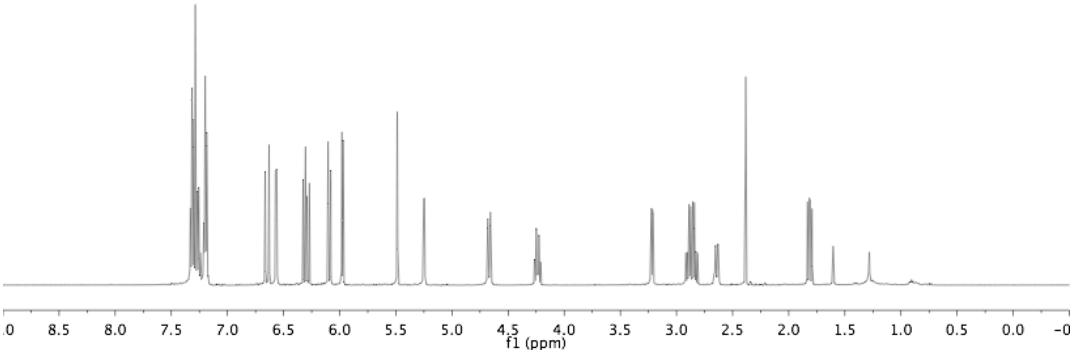


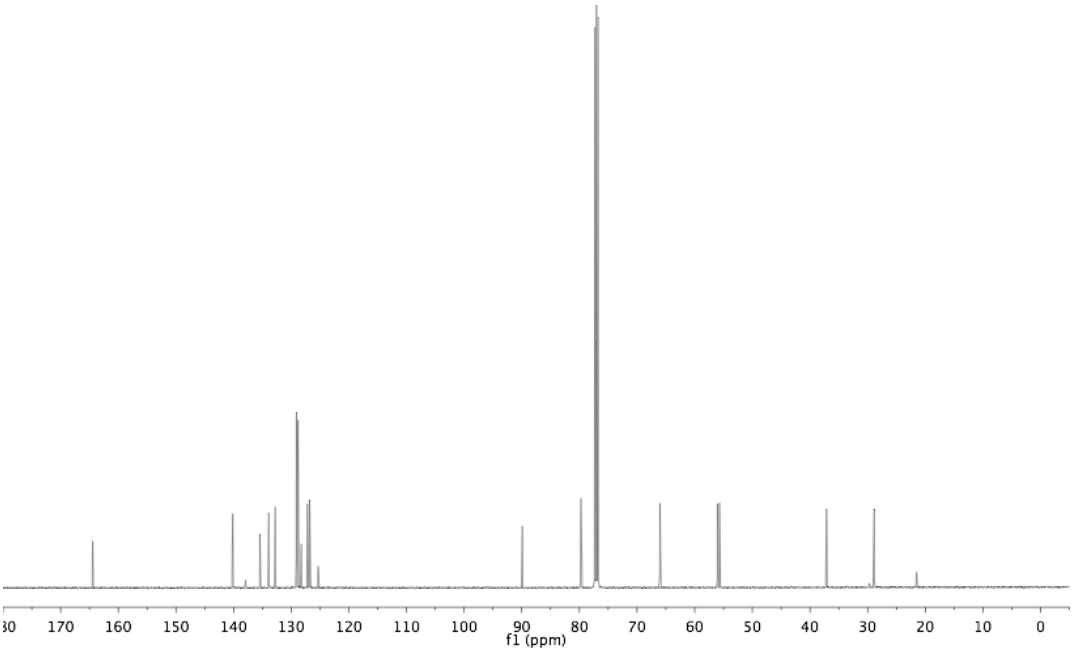




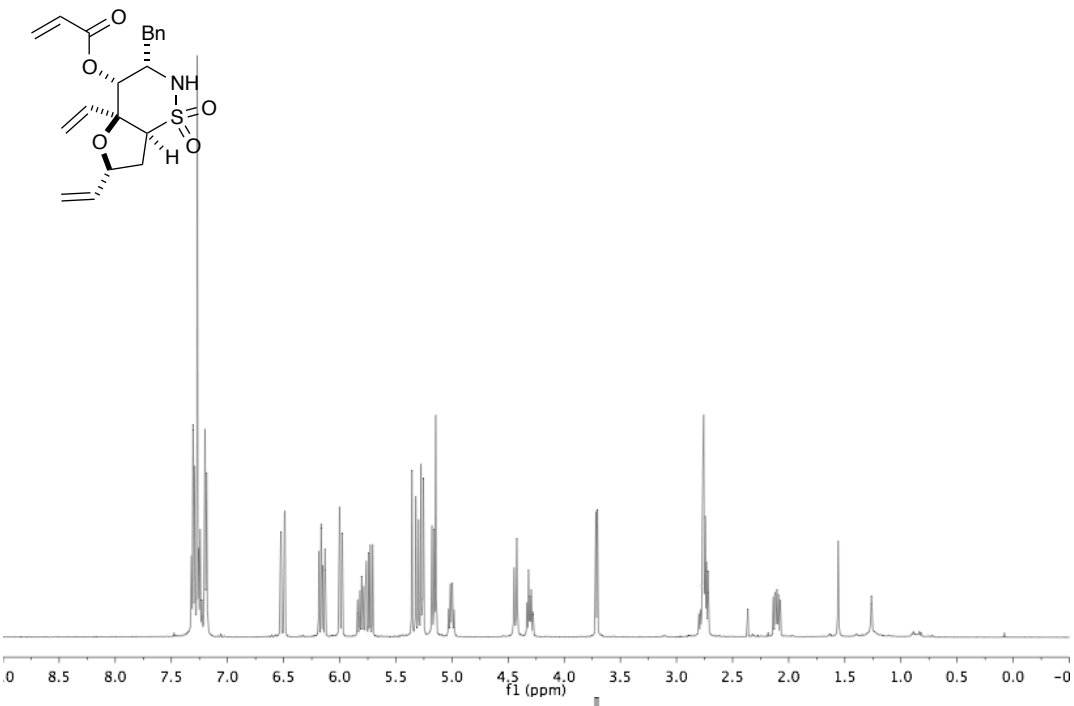
(3*S*,4*R*,4a*S*,7*R*,8a*S*)-3-Benzyl-1,1-dioxido-2,3,4,7,8,8a-hexahydro-4a,7-epoxybenzo[*e*][1,2]thiazin-4-yl acrylate (2.50)

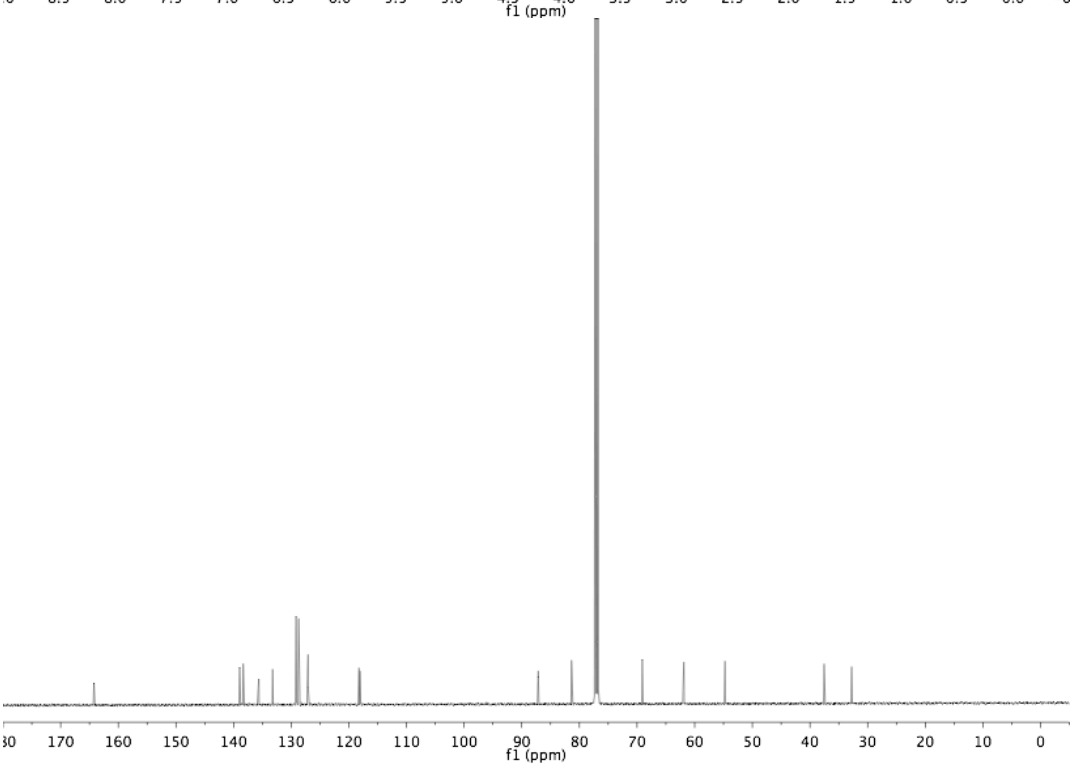




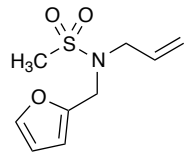


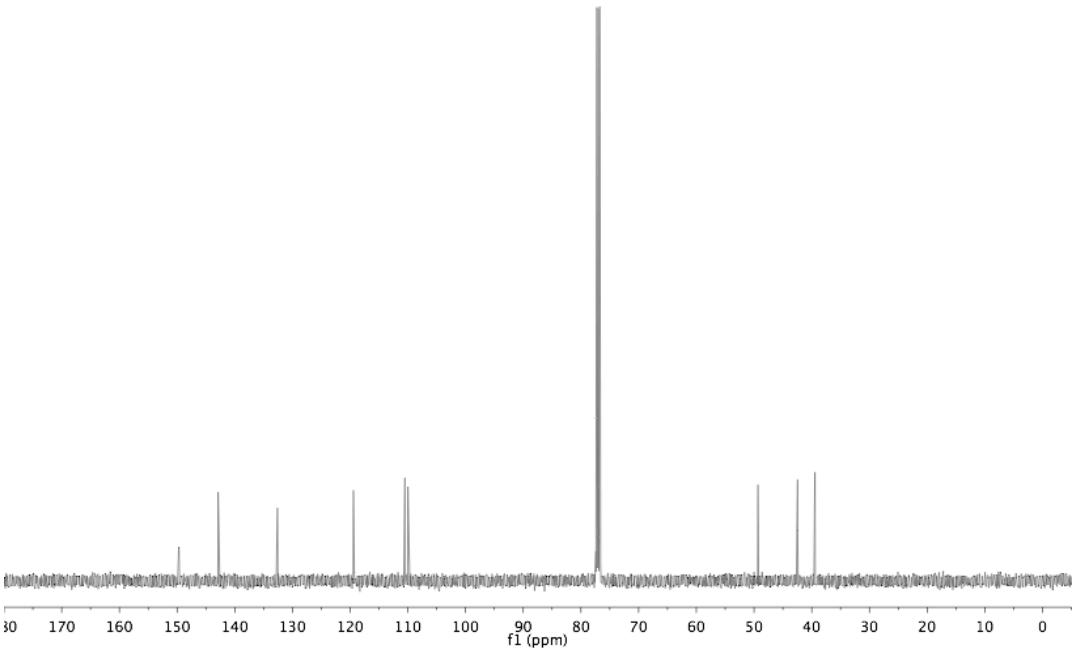
(3*S*,4*R*,4a*S*,7a*S*)-3-Benzyl-1,1-dioxido-4a,6-divinylhexahydro-2*H*-furo[2,3-*e*][1,2]thiazin-4-yl acrylate (2.51)



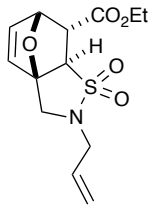


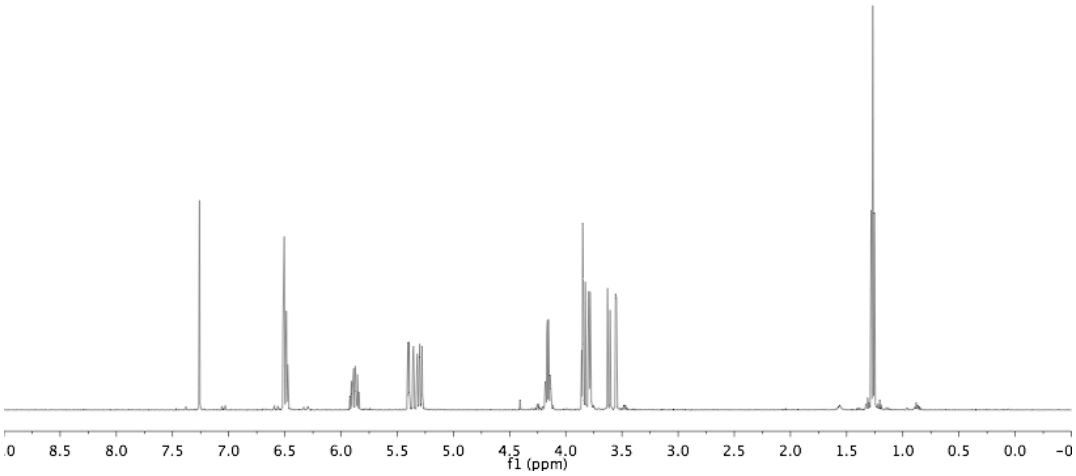
_N_-Allyl-_N_-(furan-2-ylmethyl)methanesulfonamide (2.52)

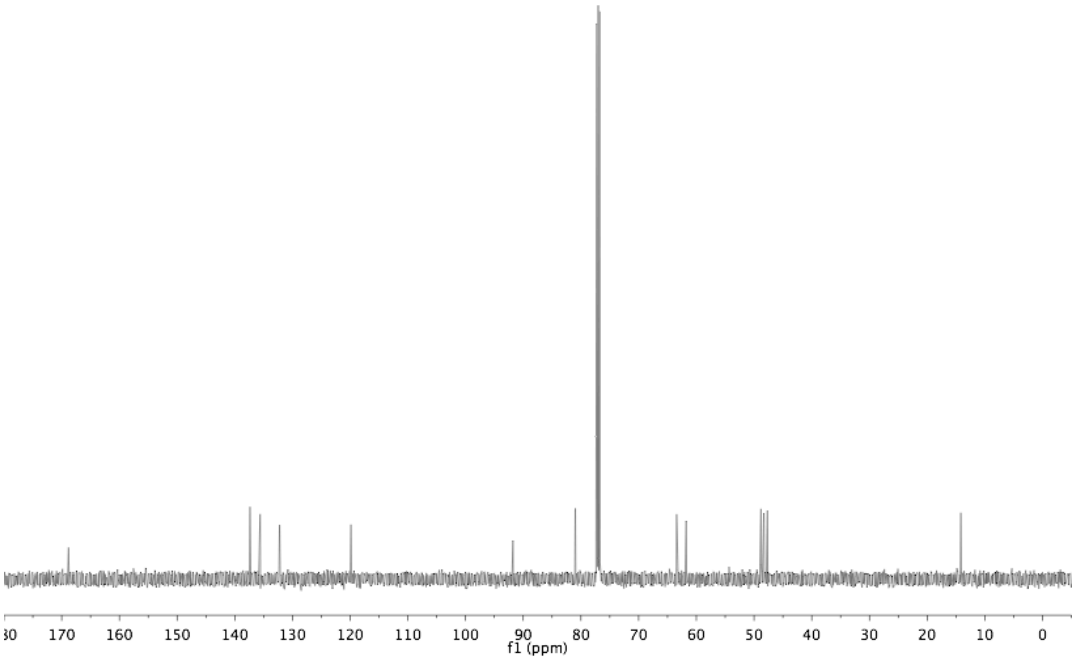




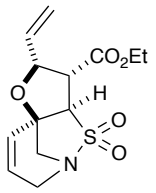
(3a*R*,6*R*,7*R*,7a*R*)-Ethyl 2-allyl-3,6,7,7a-tetrahydro-2*H*-3a,6-epoxybenzo[*d*]isothiazole-7-carboxylate 1,1-dioxide [(±)-2.55]

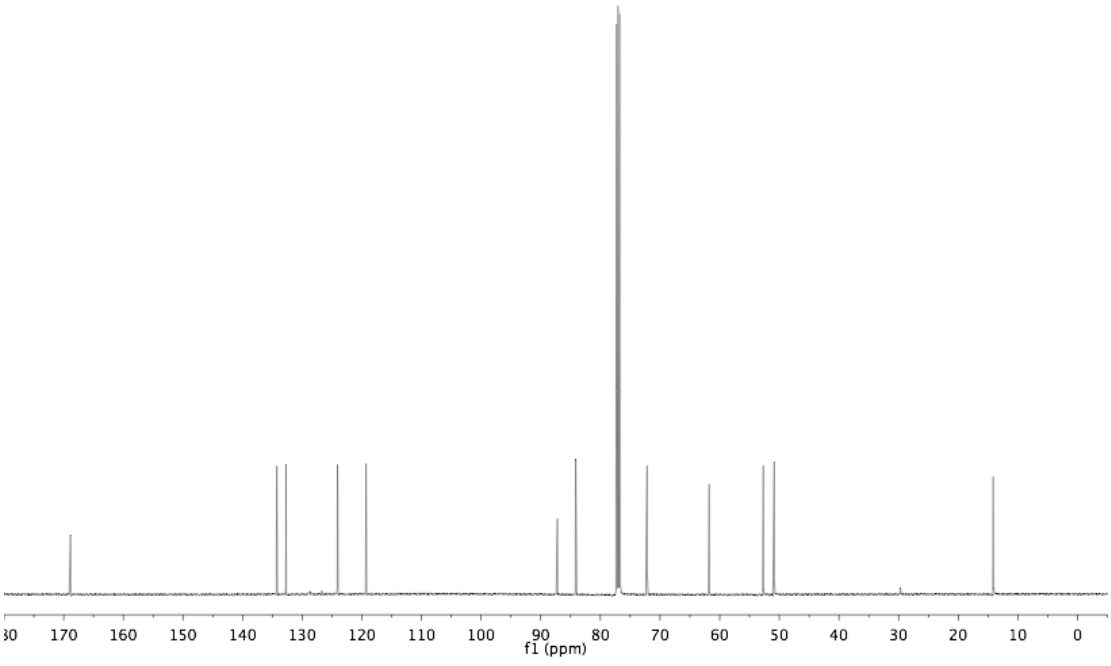




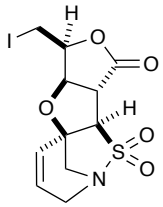


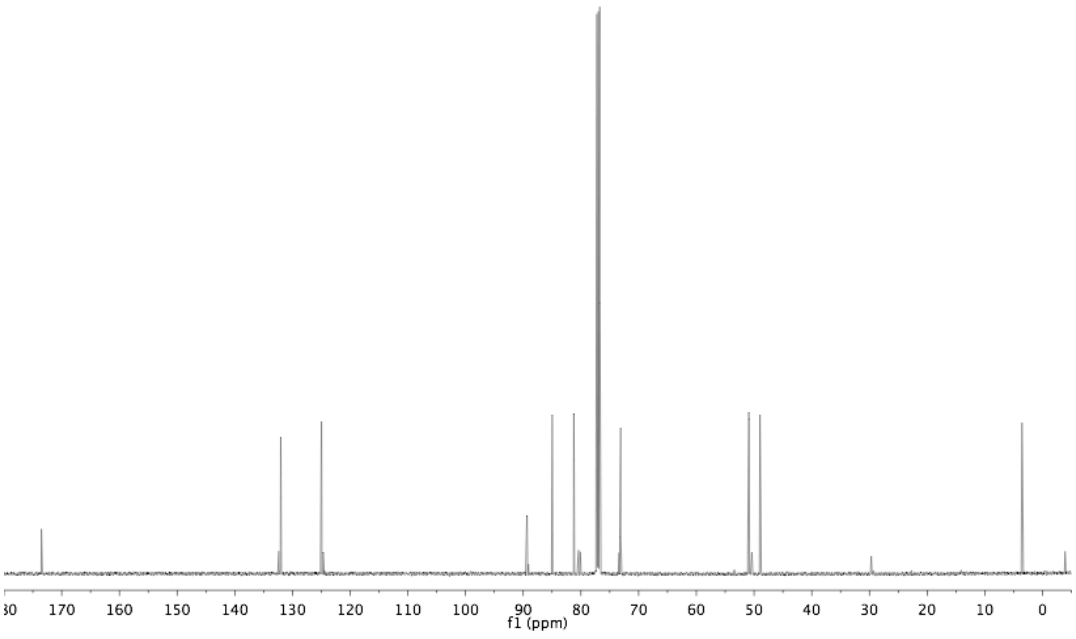
(5a*R*,7*R*,8*R*,8a*R*)-Ethyl 7-vinyl-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-*f*][1,2]thiazepine-8-carboxylate 1,1-dioxide [(±)-2.56]



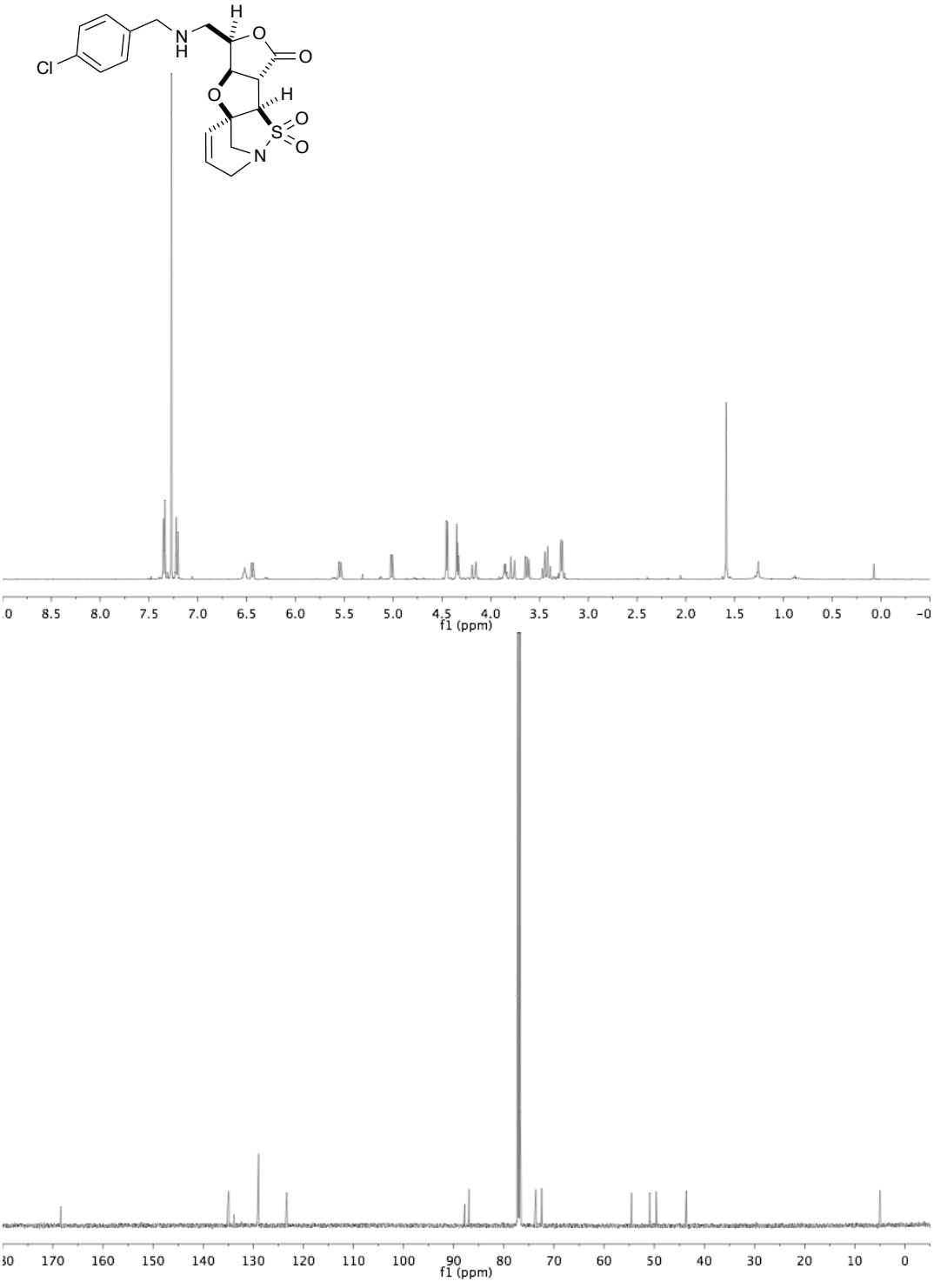


(5a*R*,6a*R*,7*S*,9a*R*,9b*R*)-7-(Iodomethyl)-6a,7,9a,9b-tetrahydro-2,5a-methanofuro[3',4':4,5]furo[2,3-*f*][1,2]thiazepin-9(3*H*)-one 1,1-dioxide [(±)-2.57]

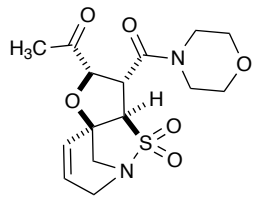


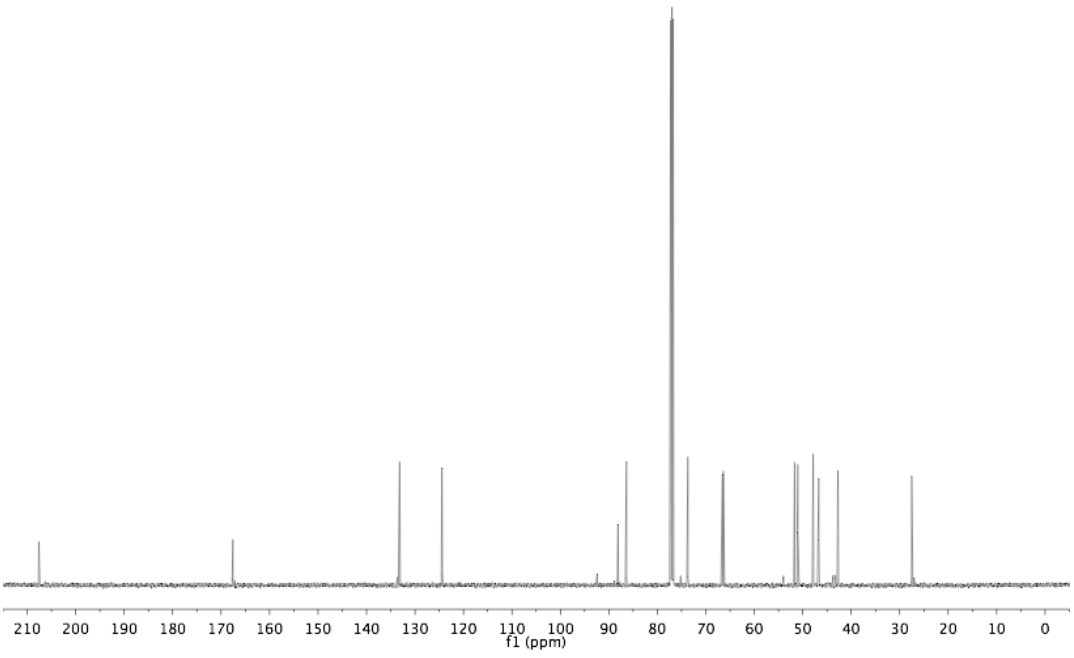


(5a*R*,6a*R*,7*R*,9a*R*,9b*R*)-7-(((4-Chlorobenzyl)amino)methyl)-6a,7,9a,9b-tetrahydro-2,5a-methanofuro[3',4':4,5]furo[2,3-*f*][1,2]thiazepin-9(3*H*)-one 1,1-dioxide [(±)-2.58]



1-((5a*R*,7*S*,8*R*,8a*R*)-8-(Morpholine-4-carbonyl)-1,1-dioxido-3,7,8,8a-tetrahydro-2,5a-methanofuro[2,3-f][1,2]thiazepin-7-yl)ethanone [(±)-2.59]





Single-Crystal X-ray Structural Studies for Compounds 2.27, 2.47 and 2.55.

Colorless crystals of $C_{11}H_{12}N_2O_3S$ (**2.27**) are, at 100(2) K, triclinic, space group $P\bar{1} - C_i^1$ (No. 2) [*1*] with **a** = 6.2228(4) Å, **b** = 8.5044(5) Å, **c** = 10.5418(6) Å, **α** = 95.101(1)°, **β** = 105.391(1)°, **γ** = 93.264(1)° ,V = 533.86(6) Å^3 and Z = 2 molecules {d_{calcd} = 1.569 g/cm^3; μ_a(MoKα) = 0.301 mm^{-1}}. Colorless crystals of $C_{15}H_{17}NO_4S$ (**2.47**) are, at 100(2) K, orthorhombic, space group $P2_12_12_1 - D_2^4$ (No. 19) [*1*] with **a** = 7.0472(3) Å, **b** = 16.252(1) Å, **c** = 25.172(1) Å, V = 2883.0(2) Å^3 and Z = 8 molecules {d_{calcd} = 1.416 g/cm^3; μ_a(MoKα) = 0.240 mm^{-1}}. Colorless crystals of $C_{13}H_{17}NO_5S$ (**2.55**) are, at 100(2) K, triclinic, space group $P\bar{1} - C_i^1$ (No. 2) [*1*] with **a** =7.0534(5) Å, **b** = 10.0416(7) Å, **c** = 10.7686(7) Å, **α** = 72.391(1)°, **β** = 86.267(1)°, **γ** = 71.551(1)° ,V = 689.22(8) Å^3 and Z = 2 molecules {d_{calcd} = 1.442 g/cm^3; μ_a(MoKα) = 0.254 mm^{-1}}. Full hemispheres of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) were measured for all three compounds using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System [*2*]. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 5323 (**2.27**), 9162 (**2.47**) and 5465 (**2.55**) reflections. Totals of 6327 (**2.27**), 34818 (**2.47**) and 8274 (**2.55**) integrated reflection intensities having 2θ((MoKα)< 60.95° (**2.27**), 2θ((MoKα)< 61.11° (**2.47**) and 2θ((MoKα)< 60.99° (**2.55**) were produced using the Bruker program SAINT[*3*]; 3103 (**2.27**), 8614 (**2.47**) and 4040 (**2.55**) of these were unique and gave R_{int} = 0.029 (**2.27**), R_{int} = 0.051 (**2.47**) and R_{int} = 0.032 (**2.55**) with a coverage which was at least 95.6% complete. The data were corrected empirically for variable absorption effects using equivalent reflections. The relative transmission factors ranged from 0.925 to 1.000 for (**2.27**), from 0.919 to 1.000 for (**2.47**) and from 0.851 to 1.000 for (**2.55**). The Bruker software package SHELXTL was used to solve all three structures using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package

[*4*].

All hydrogen atoms for all three structures were located from difference Fouriers and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. The final structural models for all three compounds incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms.

A total of 202 parameters were refined for **2.27** using no restraints, 3103 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0552\ P)^2 + 0.208\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence for **2.27** are: R_1(unweighted, based on F) = 0.032 for 2991 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 60.95°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.033 and wR_2(weighted, based on F^2) = 0.089 for all 3103 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 60.95°$. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference Fourier for **5** had maxima and minima of 0.49 $e^-/Å^3$ and -0.39 $e^-/Å^3$, respectively.

A total of 515 parameters were refined for **2.47** using no restraints, 8614 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0377\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence for **2.47** are: R_1(unweighted, based on F) = 0.040 for 7746 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 61.11°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.045 and wR_2(weighted, based on F^2) = 0.080 for all 8614 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 61.11°$. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference Fourier for **2.47** had maxima and minima of 0.51 $e^-/Å^3$ and -0.34 $e^-/Å^3$, respectively. The absolute configuration for **2.47** was determined experimentally using anomalous dispersion of the x-rays; the "Flack absolute structure" parameter refined to a final value of 0.03(4).

A total of 249 parameters were refined for **2.55** using no restraints, 4040 data

and weights of $w = 1/ [\sigma^2(F^2) + (0.0651\ P)^2 + 0.126\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence for **2.55** are: R_1(unweighted, based on F) = 0.038 for 3724 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 60.99°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.041 and wR_2(weighted, based on F^2) = 0.105 for all 4040 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 60.99°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference Fourier for **2.55** had maxima and minima of 0.63 $e^-/Å^3$ and -0.32 $e^-/Å^3$, respectively.

Acknowledgment

The authors thank the National Science Foundation (grant CHE-0923449) and the University of Kansas for funds to purchase the X-ray instrument and computers.

References

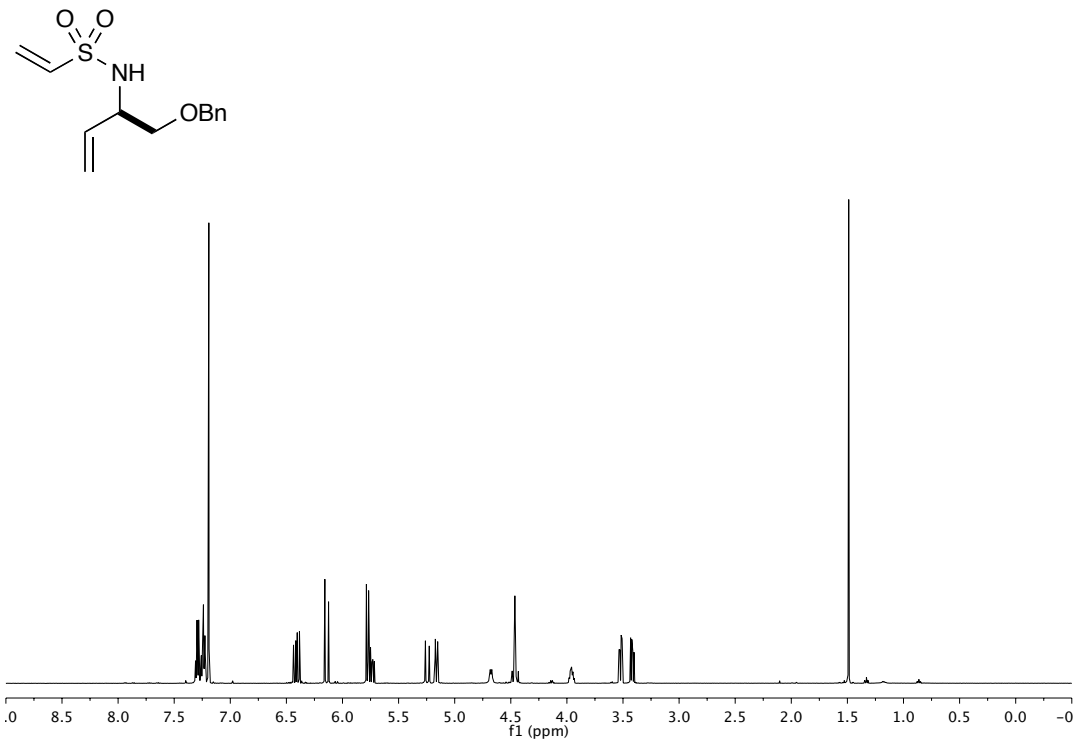
(1) International Tables for Crystallography, Vol A, 4th ed., Kluwer: Boston (1996).

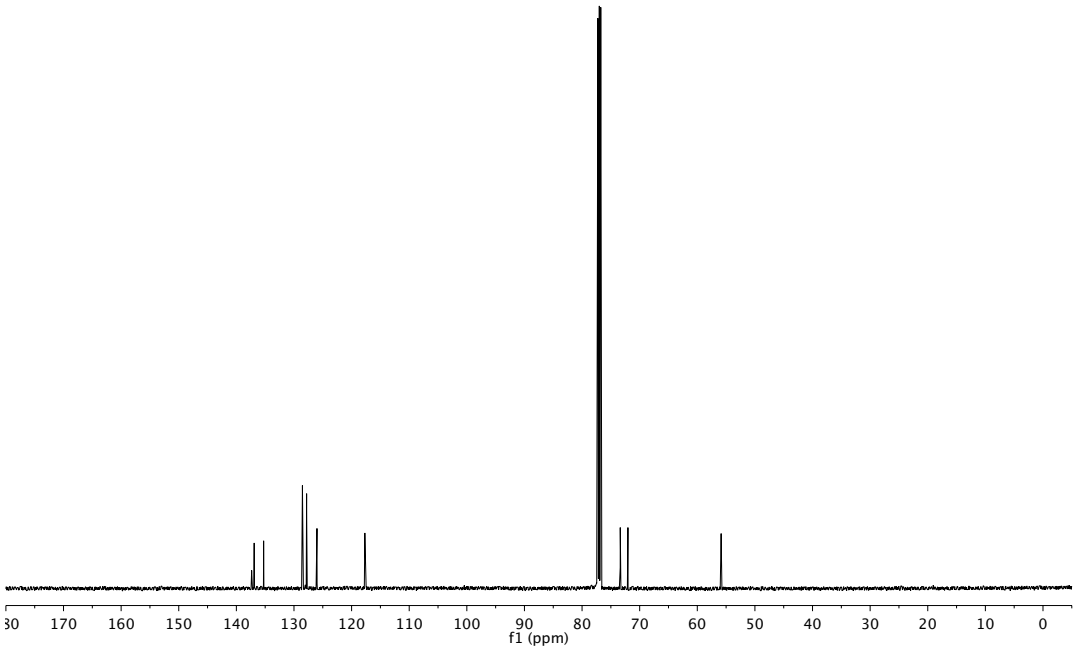
(2) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711–5373 USA.

(3) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719–1173, USA.

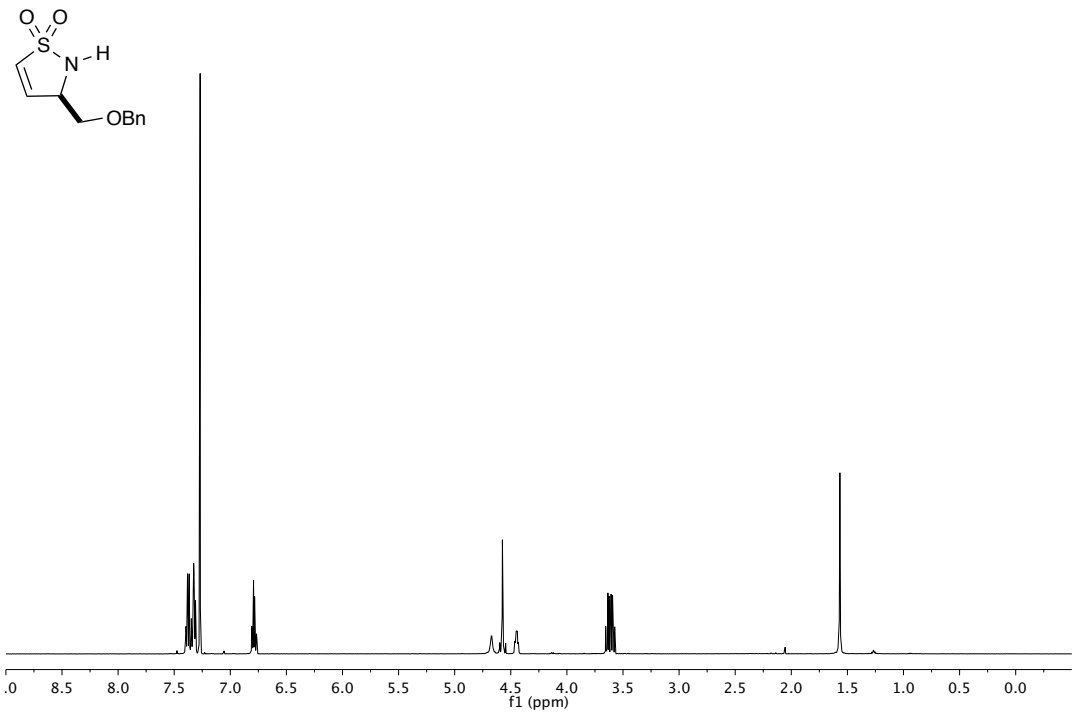
(4) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711–5373 USA.

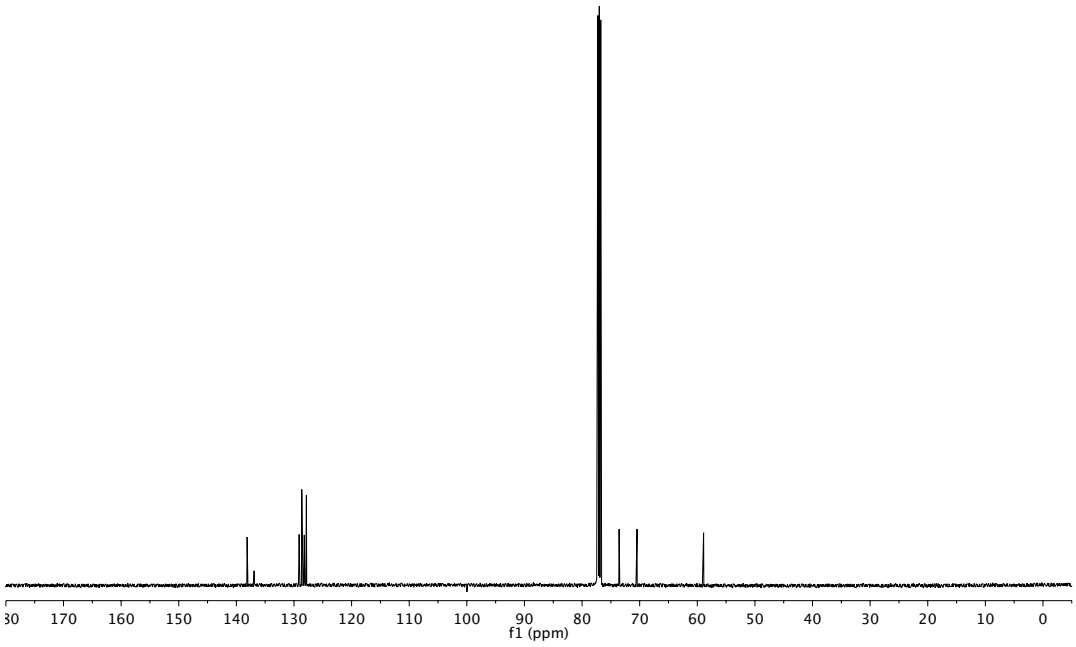
(*R*)-*N*-(1-(Benzyloxy)but-3-en-2-yl)ethenesulfonamide



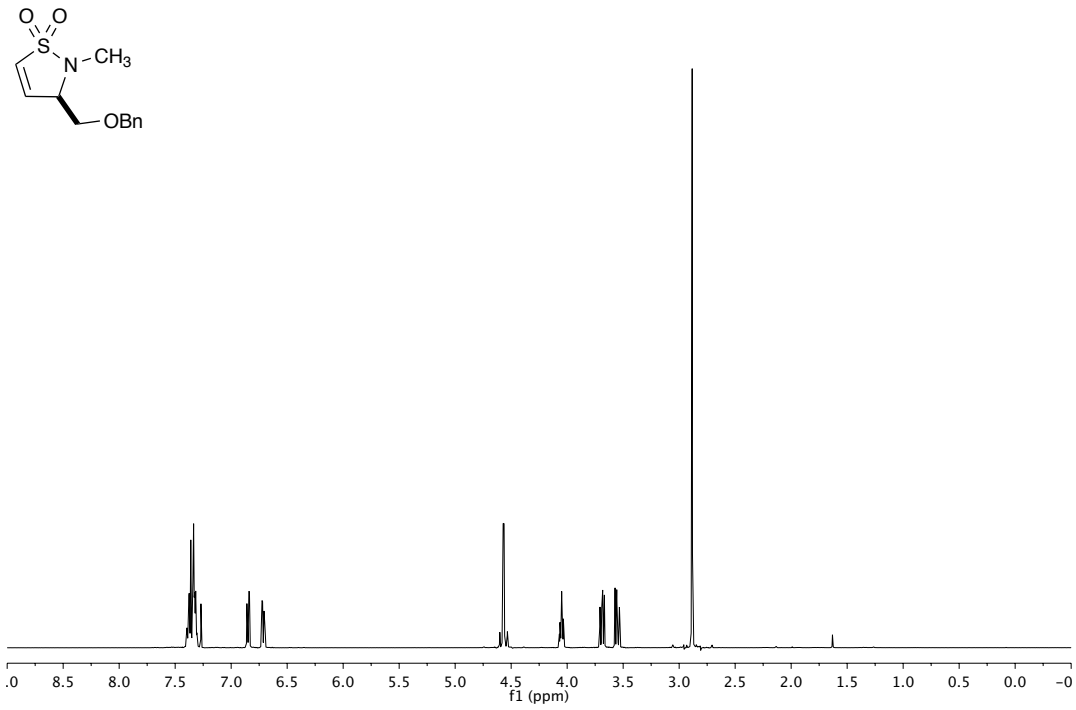


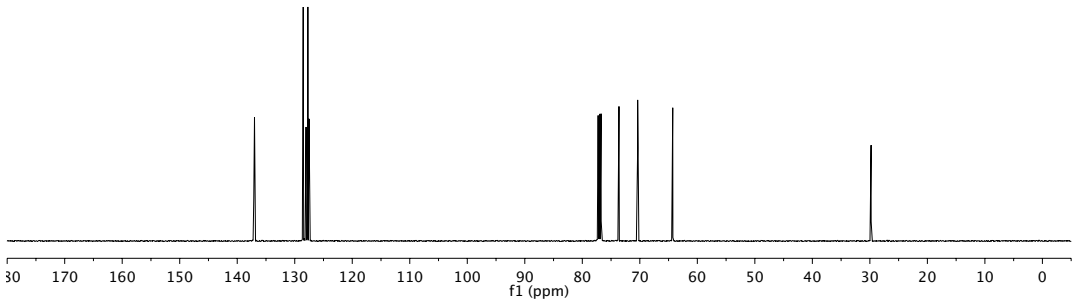
(*R*)-3-((Benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide [(*R*)-3.3]



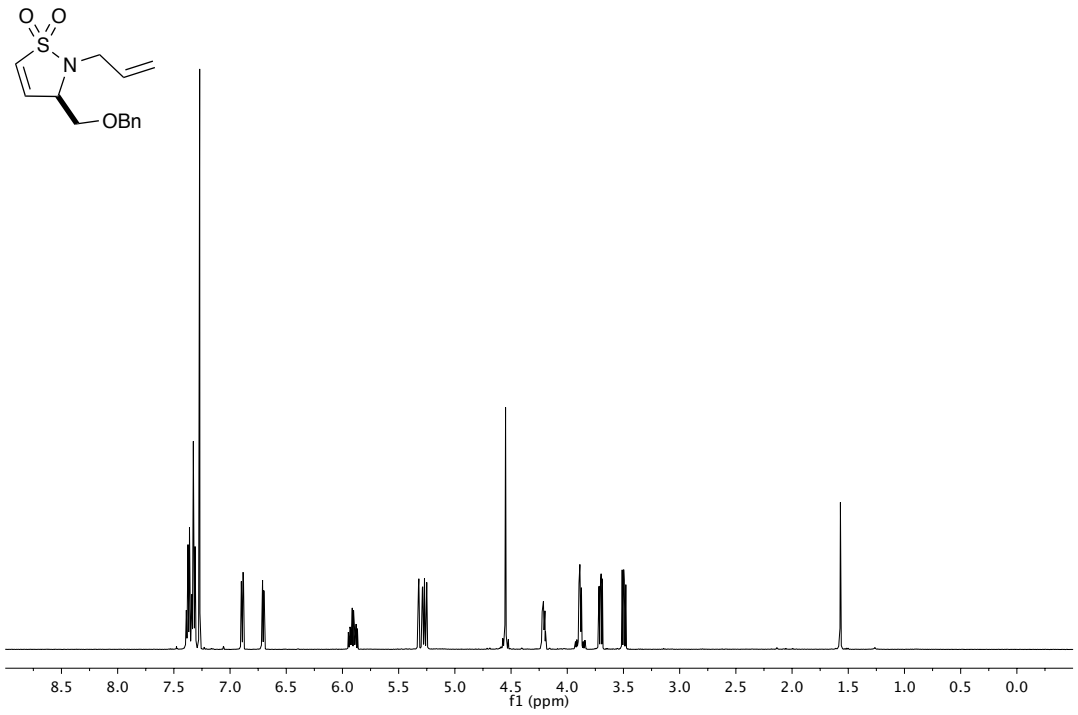


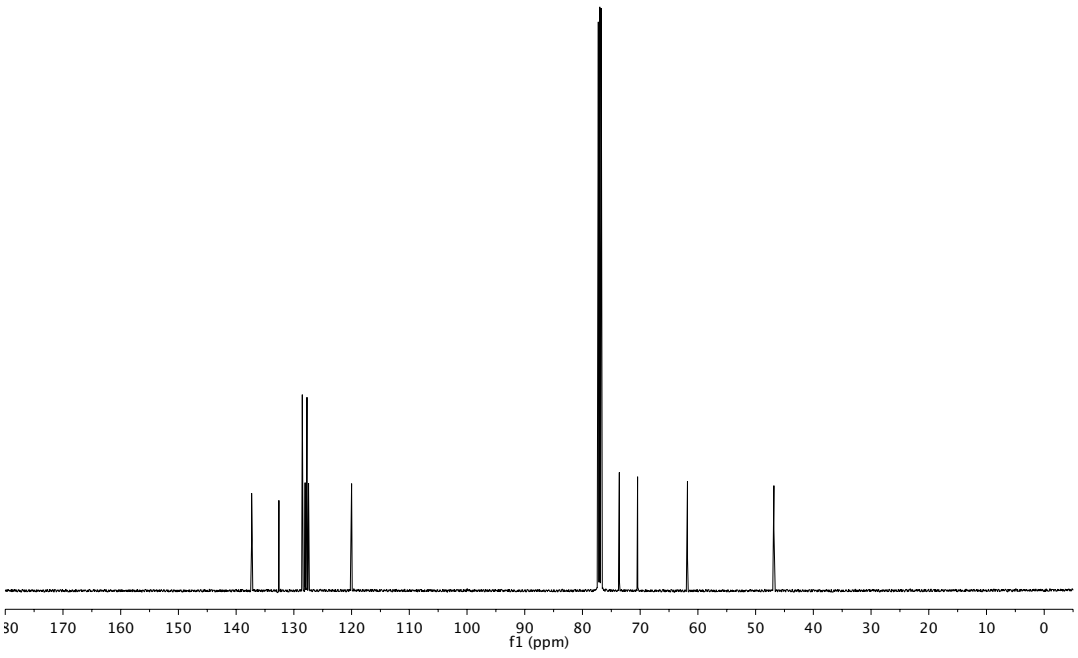
(*R*)-3-((Benzyloxy)methyl)-2-methyl-2,3-dihydroisothiazole 1,1-dioxide (3.4)



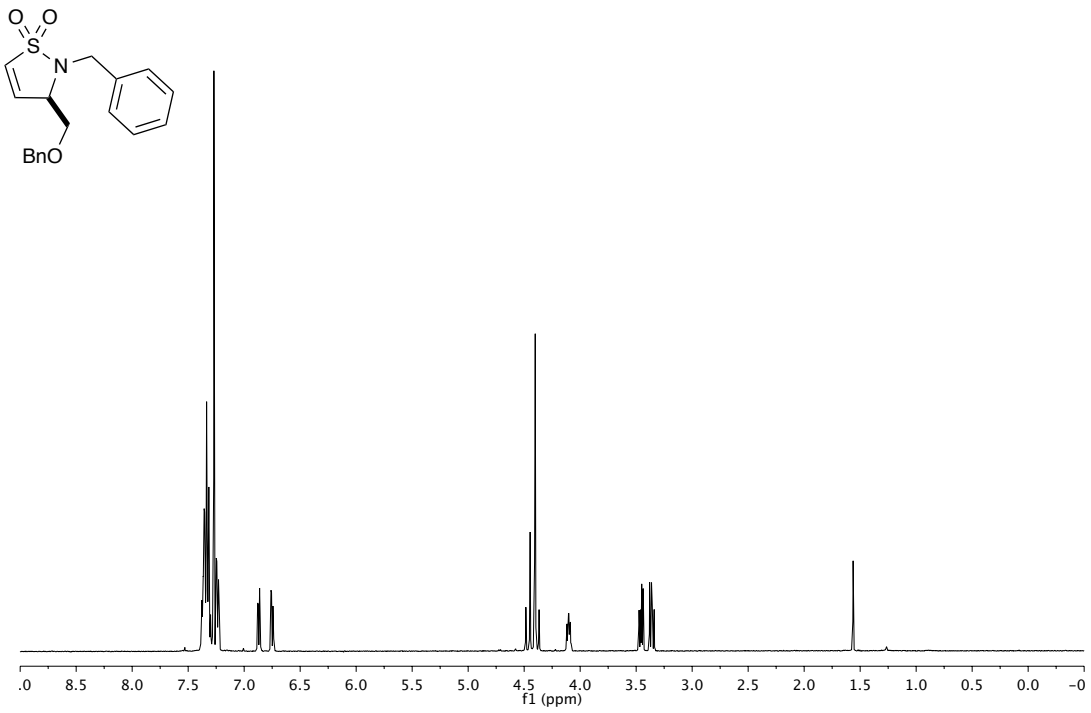


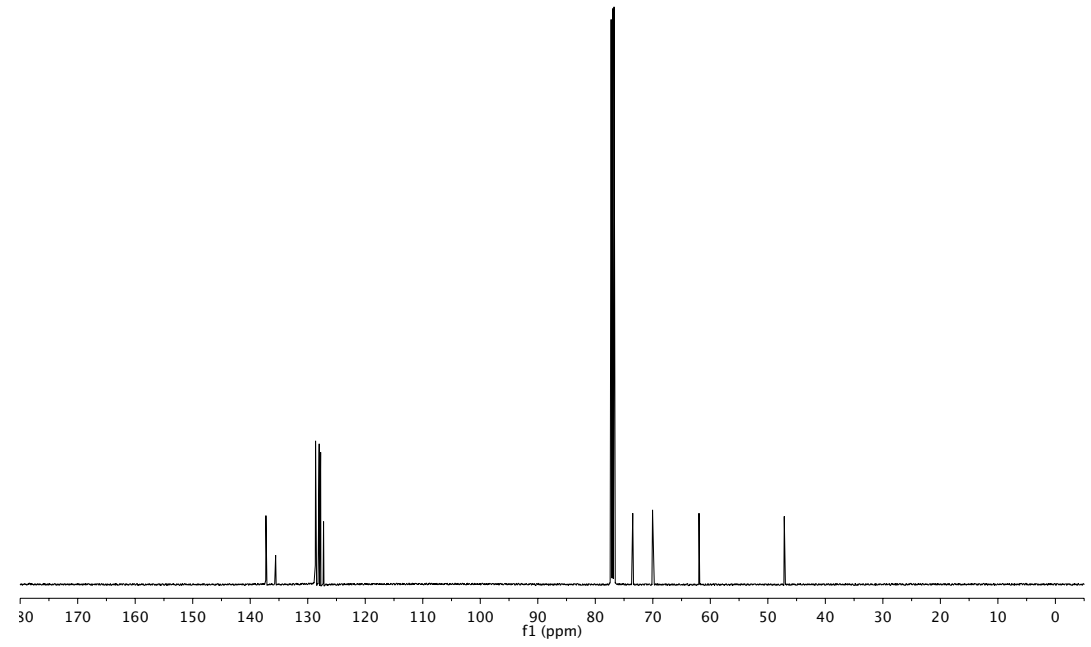
(*R*)-2-Allyl-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.5)



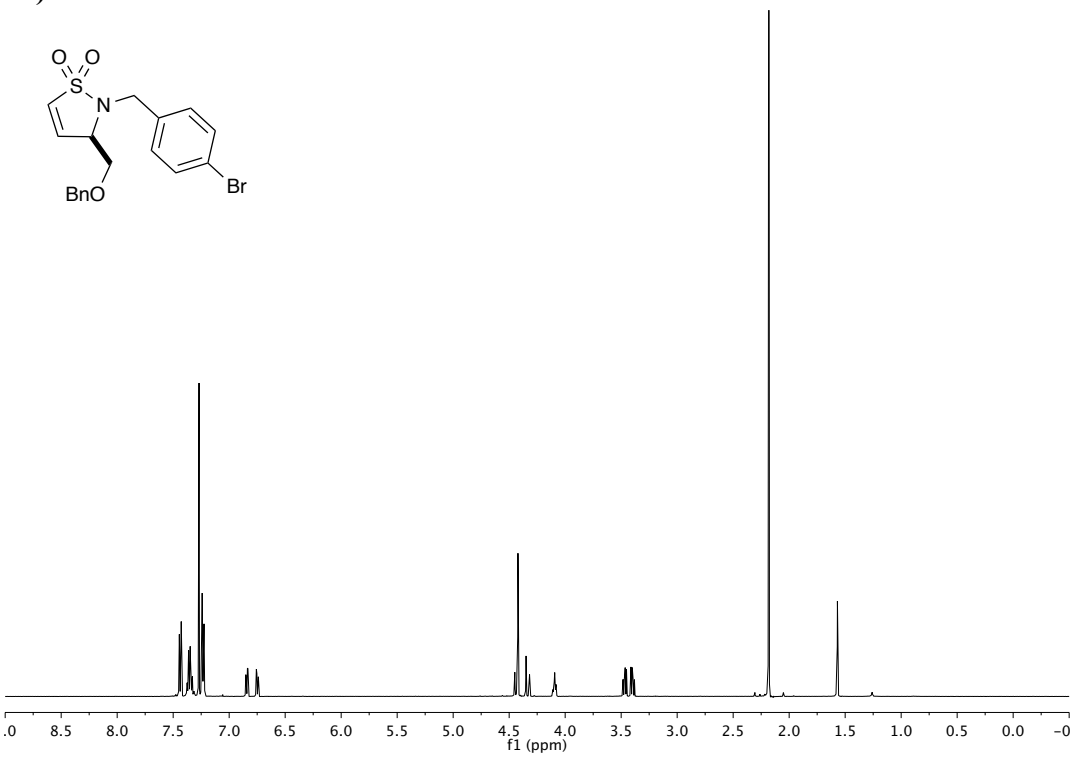


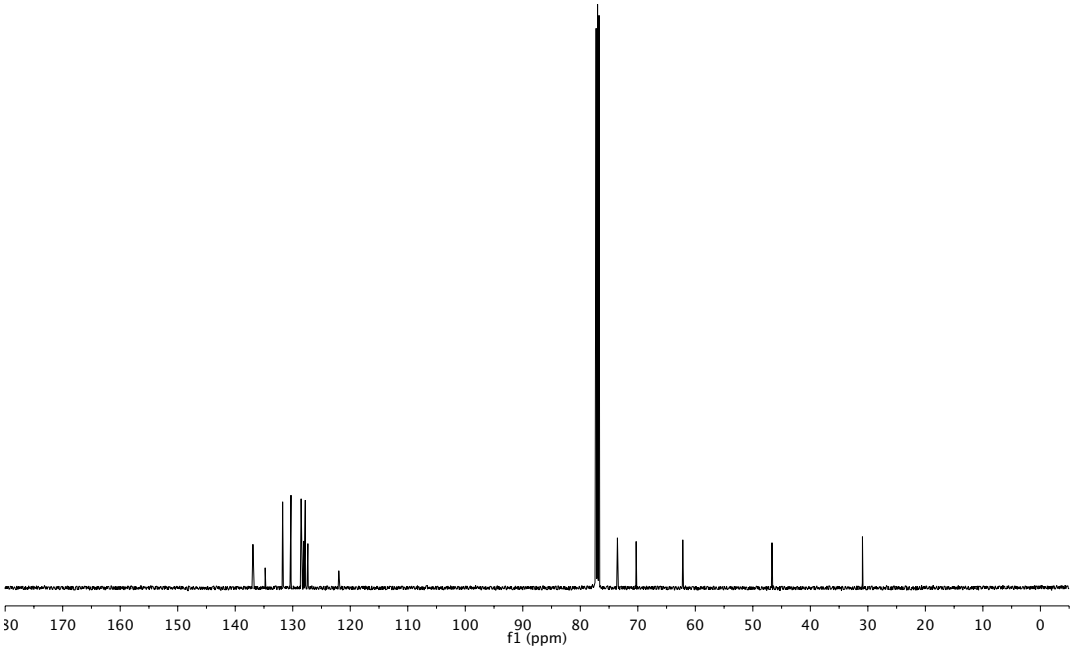
(*R*)-2-Benzyl-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.6)



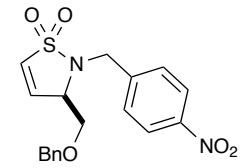


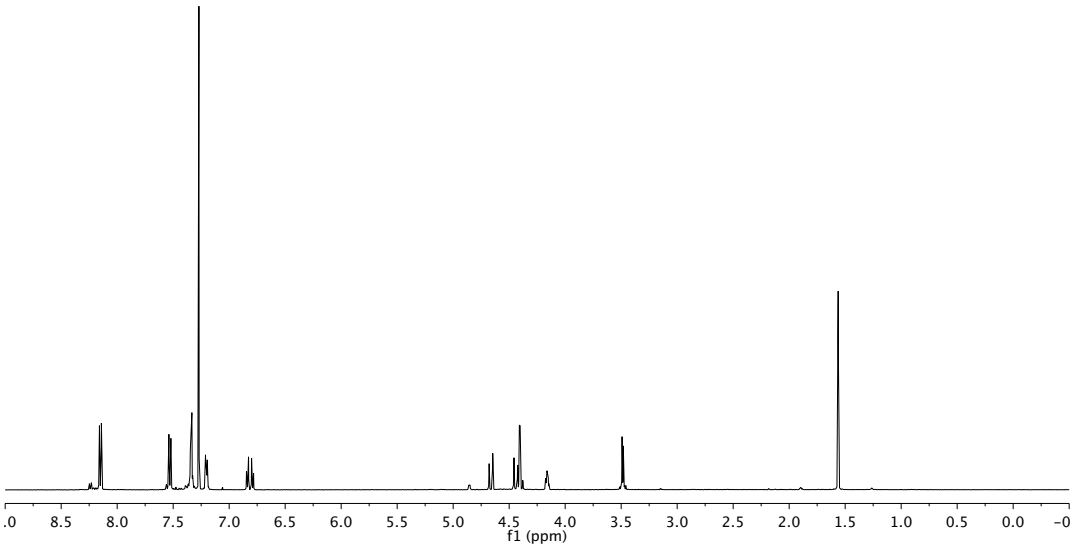
(*R*)-3-((Benzyloxy)methyl)-2-(4-bromobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.7)

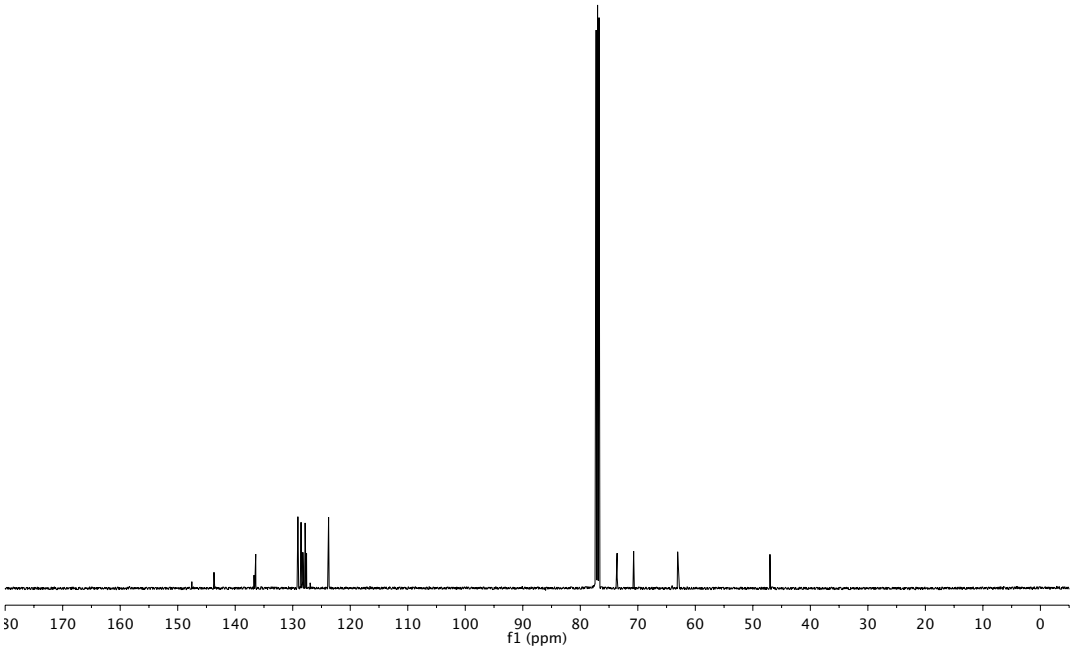




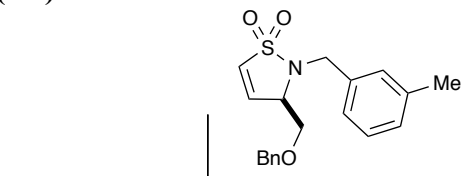
(*R*)-3-((Benzyloxy)methyl)-2-(4-nitrobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.8)

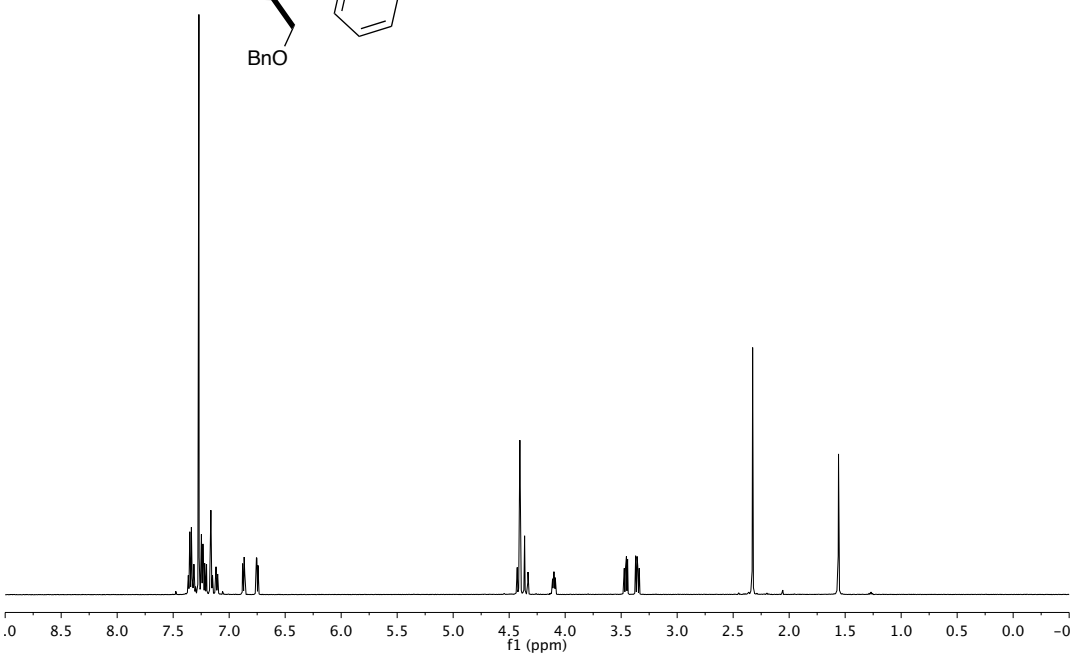


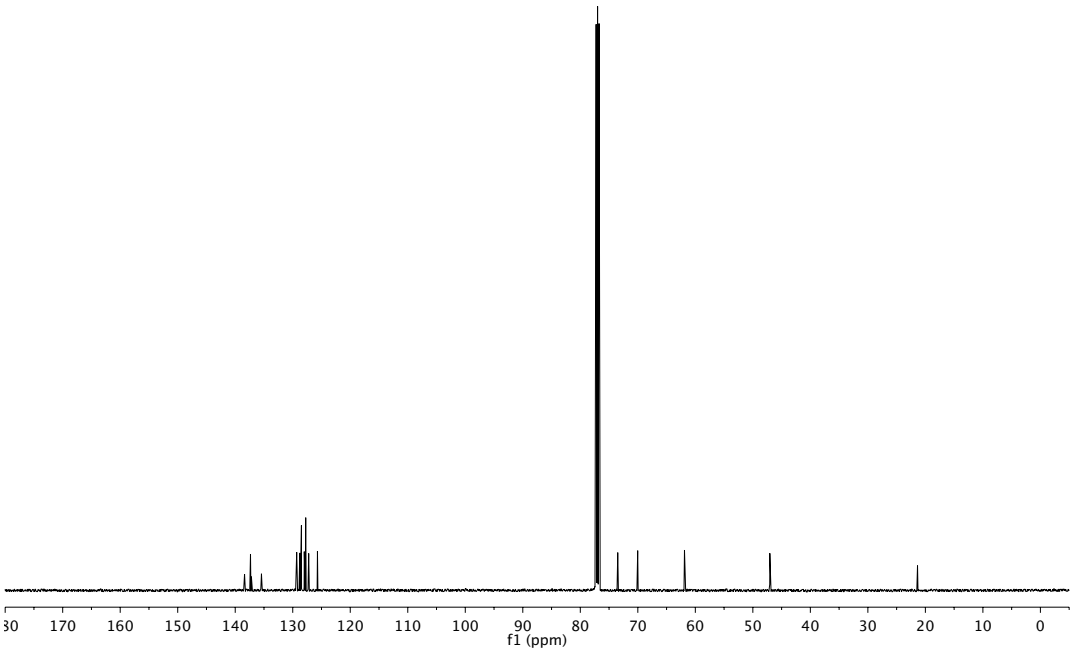




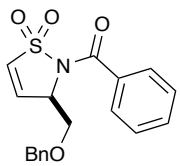
(*R*)-3-((Benzyloxy)methyl)-2-(3-methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.9)

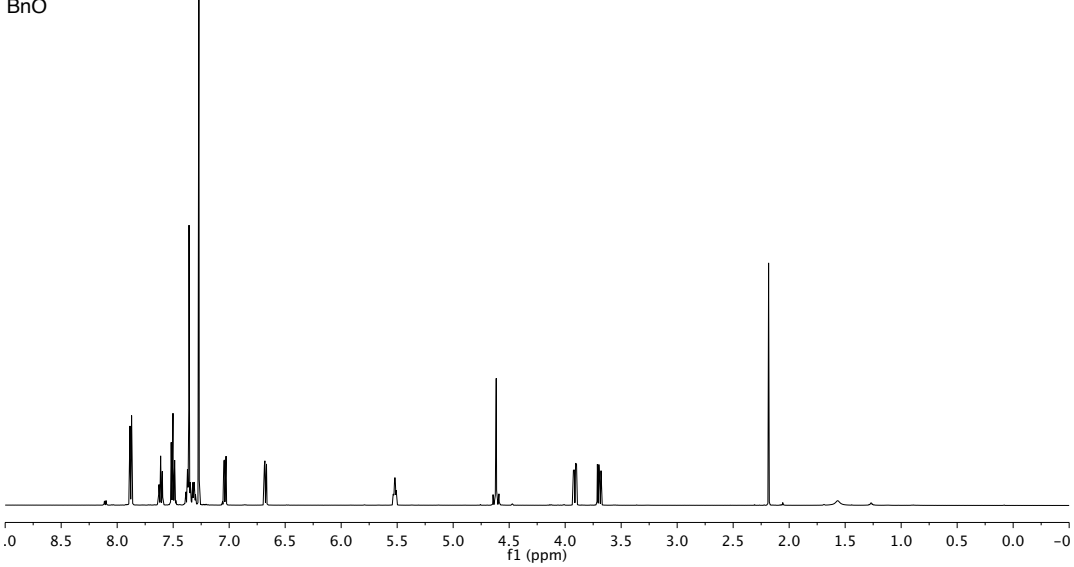


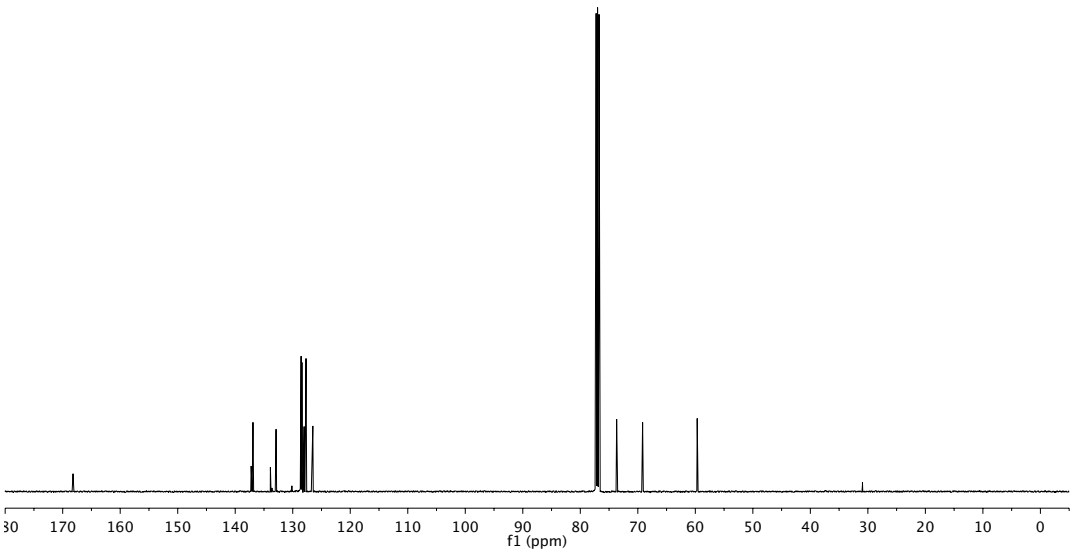




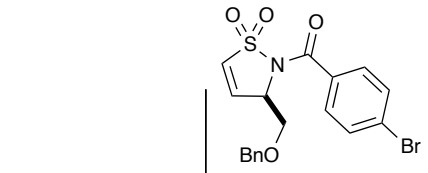
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(phenyl)methanone (3.10)

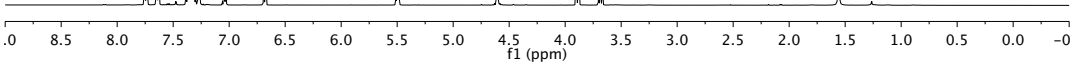


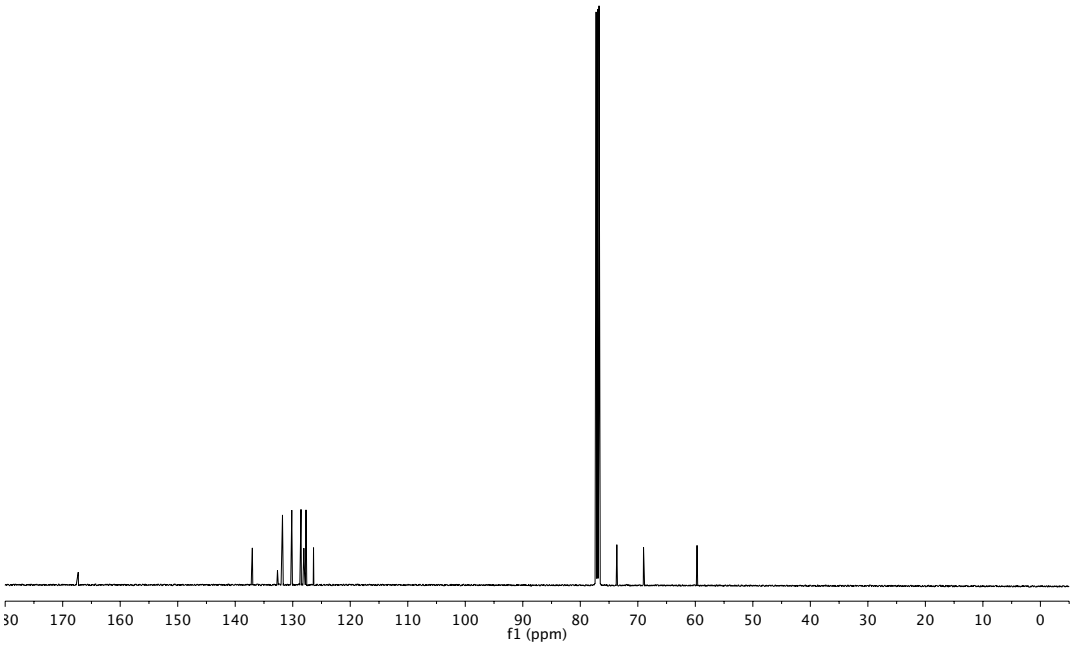




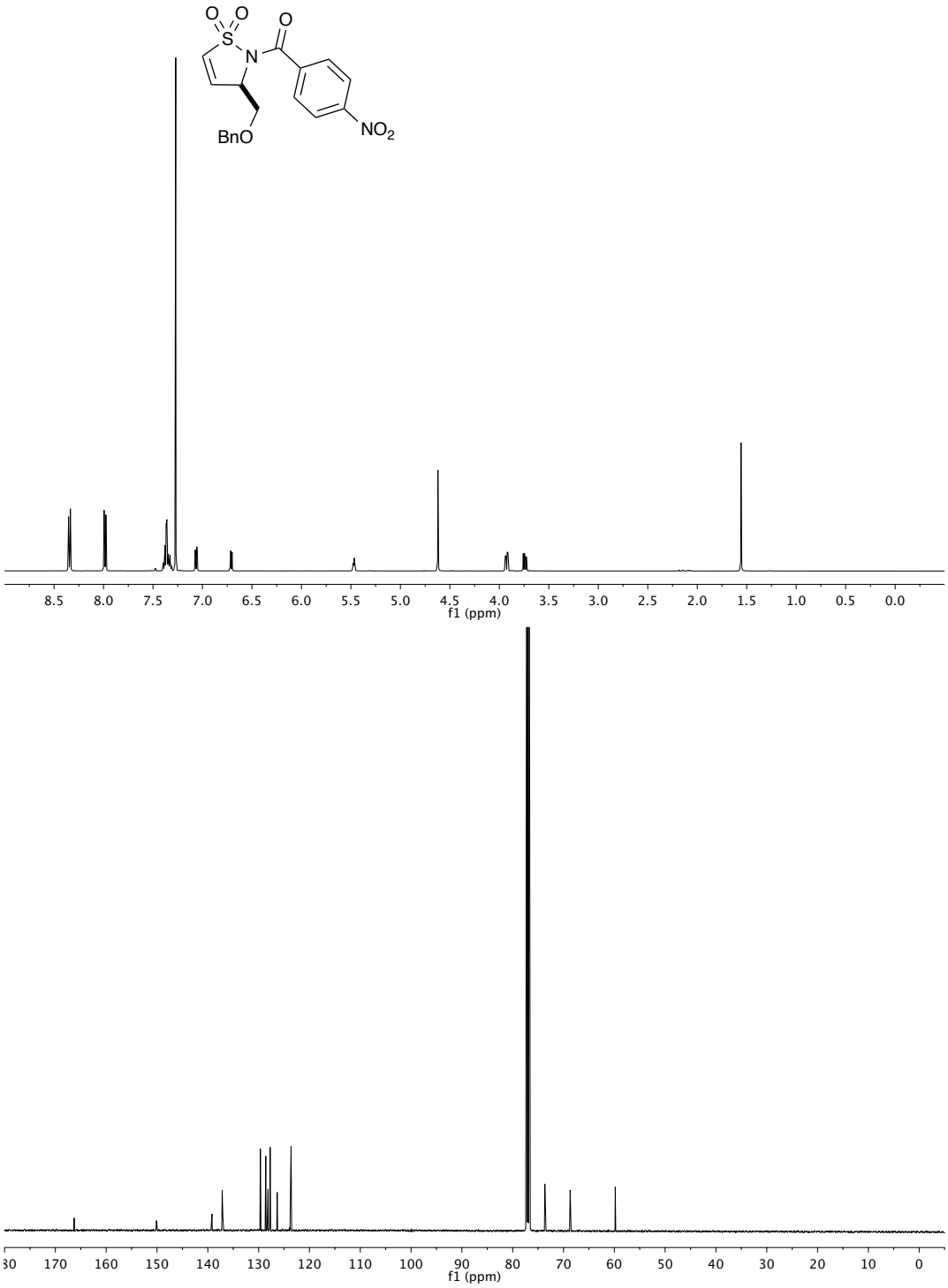
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-bromophenyl)methanone (3.11)



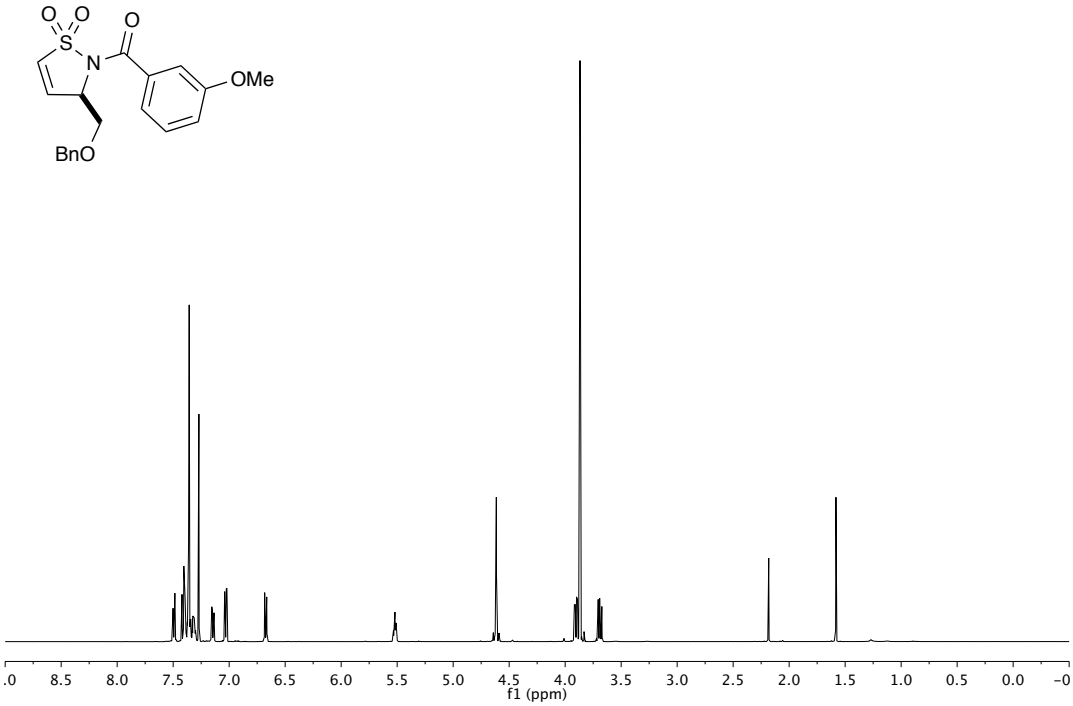


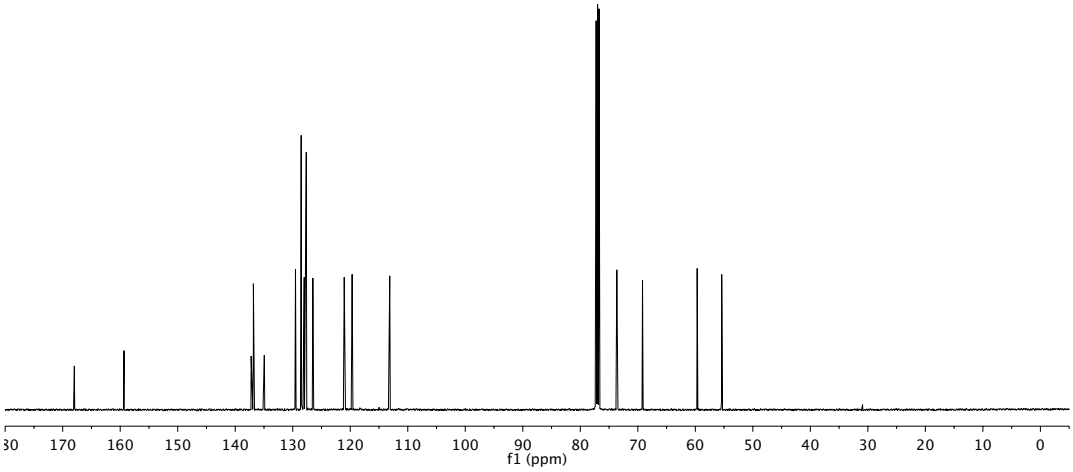


(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-nitrophenyl)methanone (3.12)

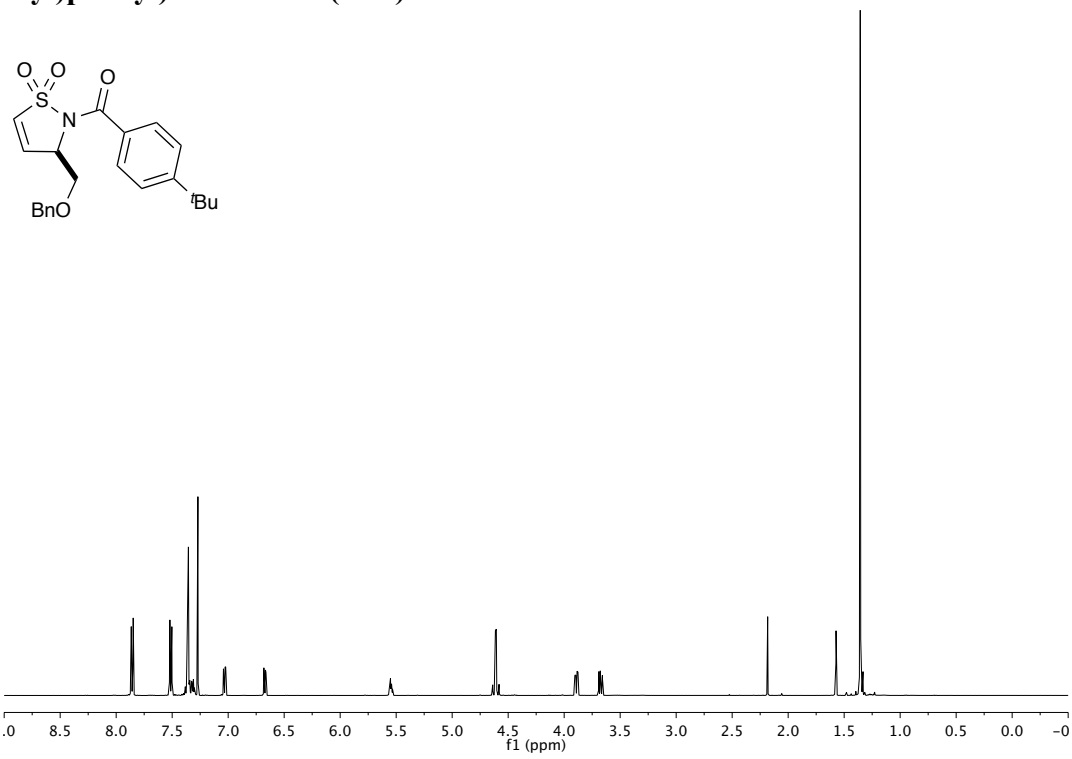


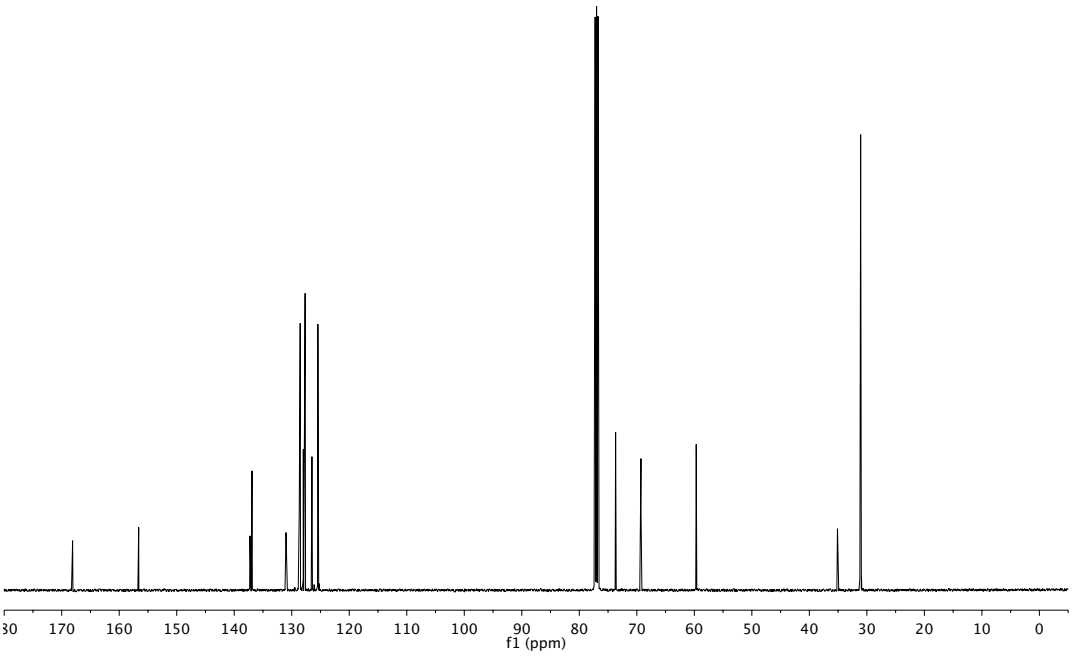
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(3-methoxyphenyl)methanone (3.13)



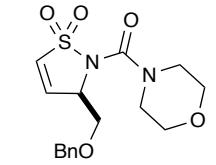


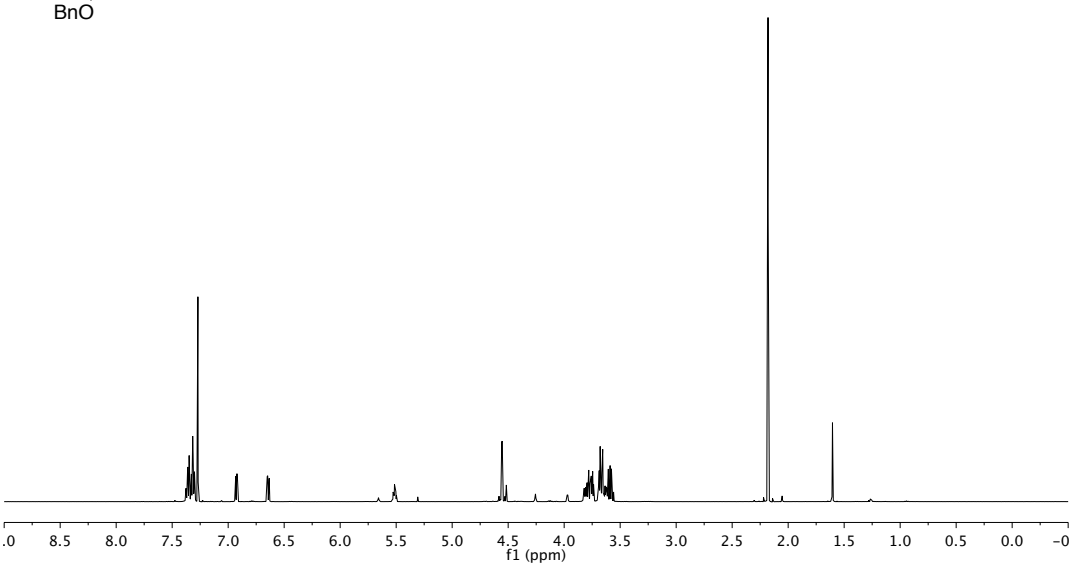
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-(*tert*-butyl)phenyl)methanone (3.14)

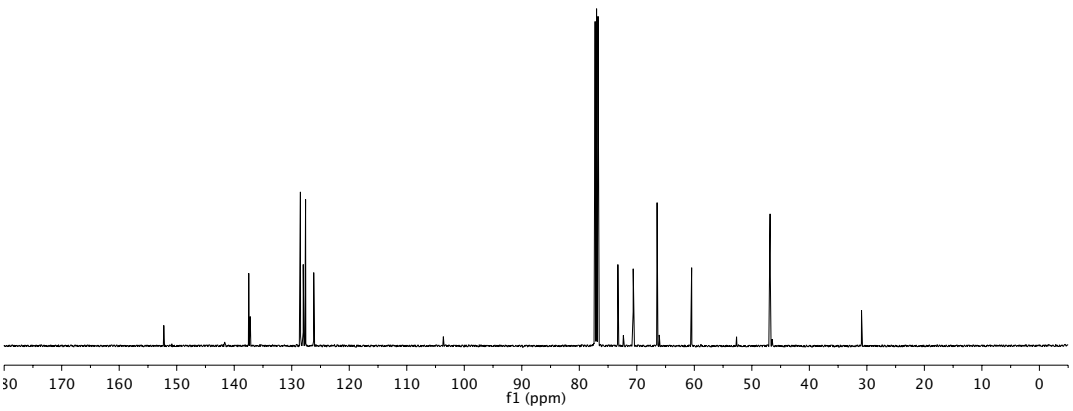




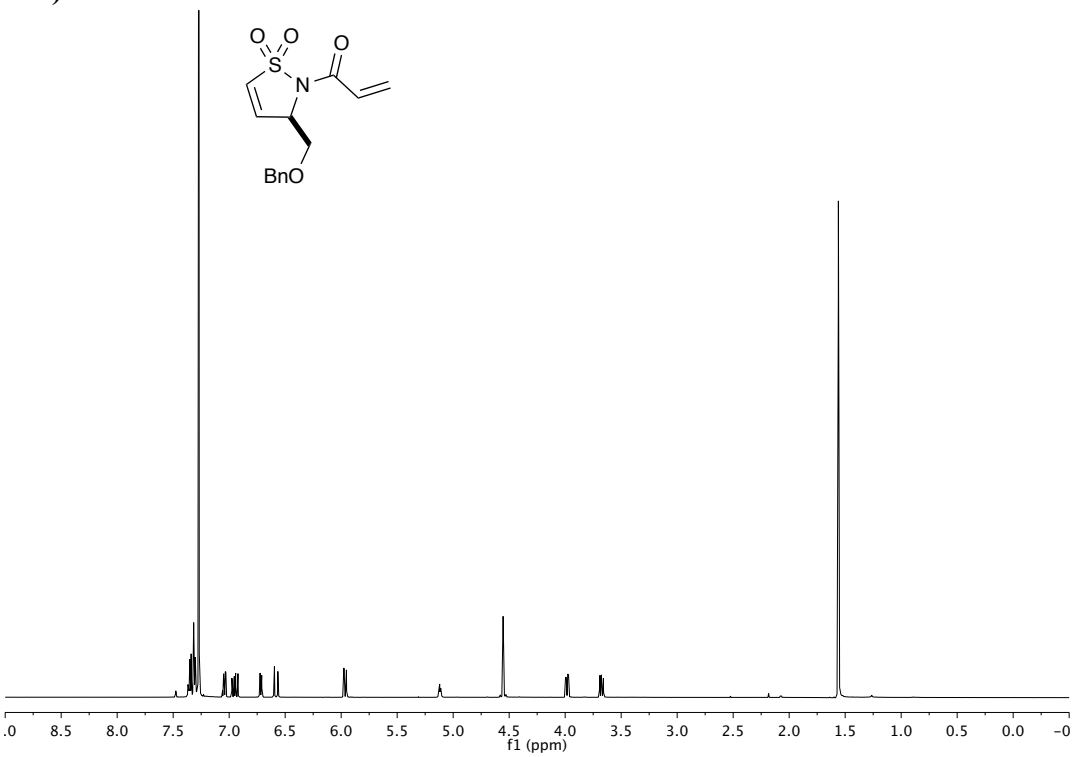
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(morpholino)methanone (3.15)

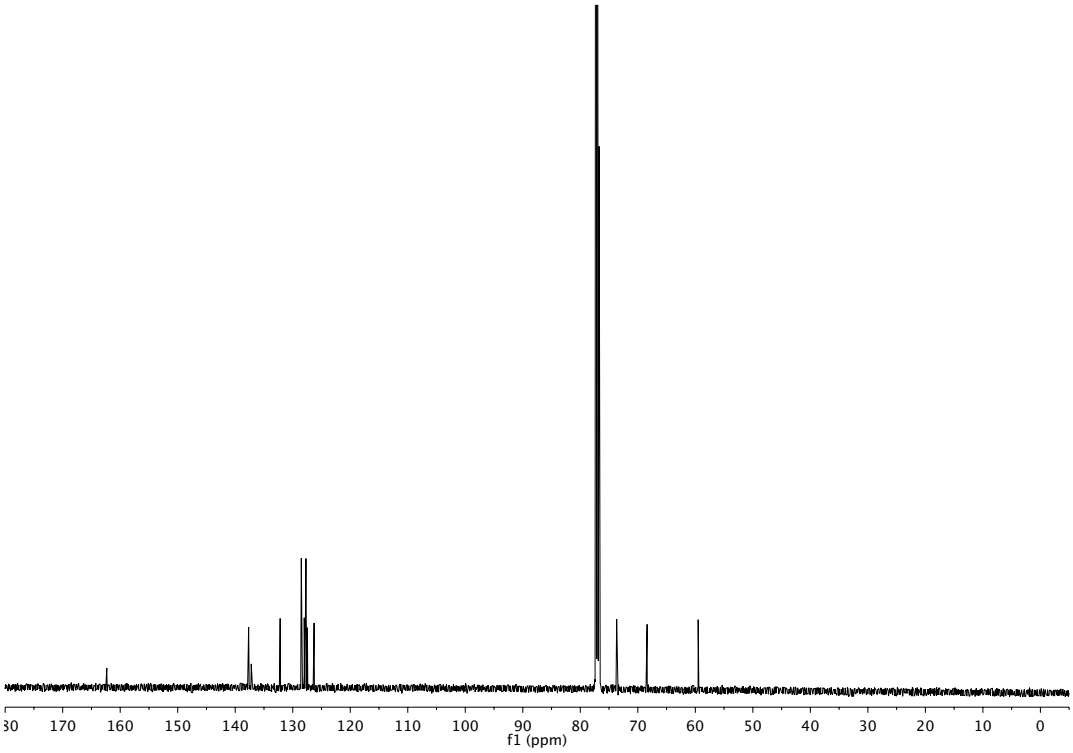




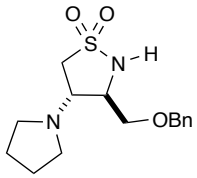


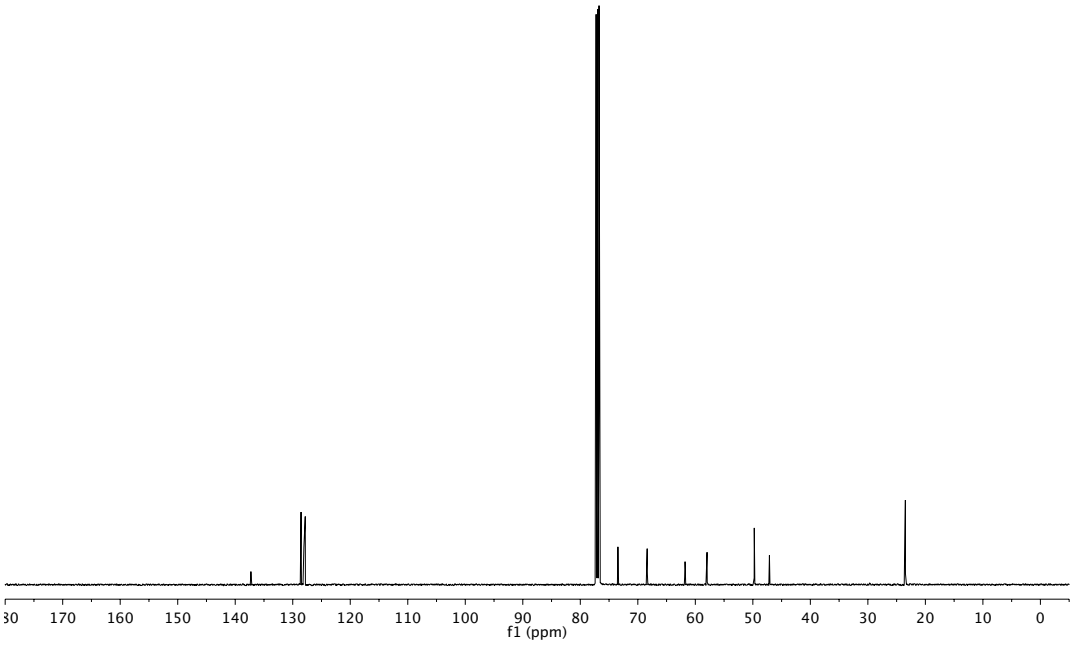
(*R*)-1-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)prop-2-en-1-one (3.16)



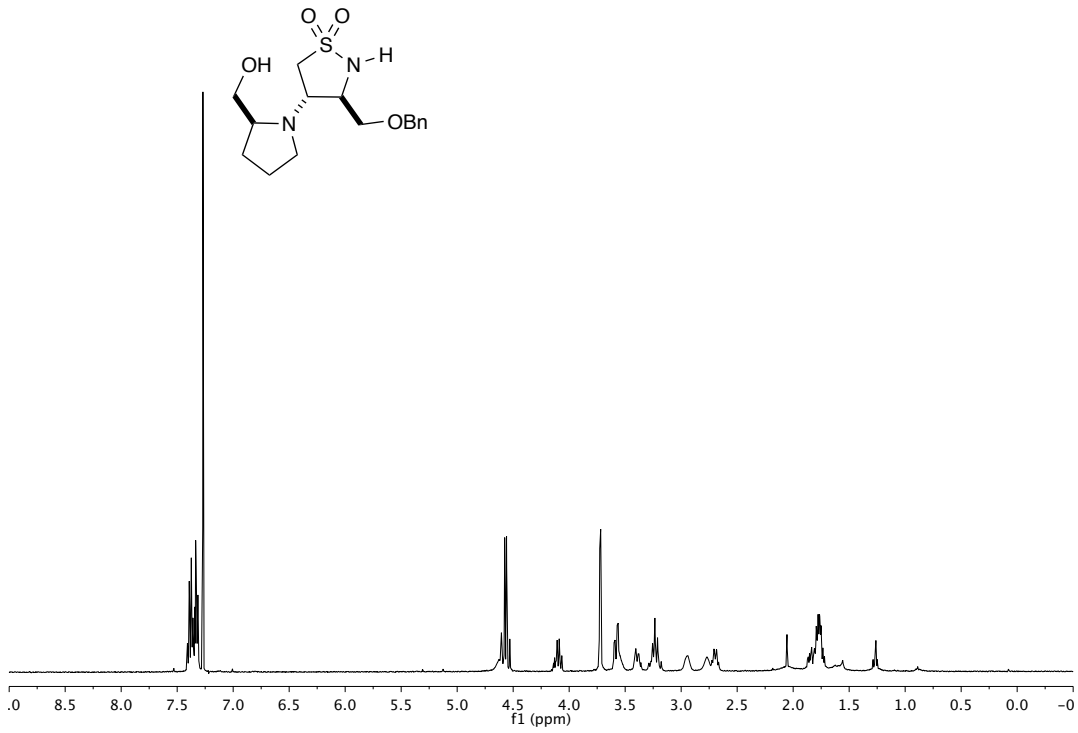


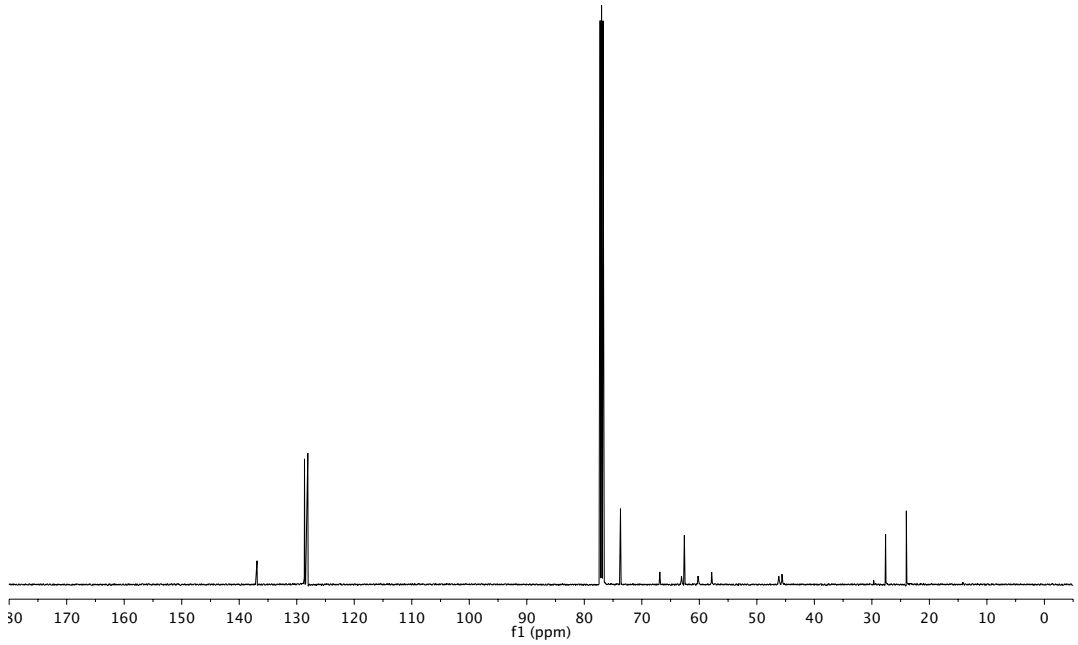
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.17)



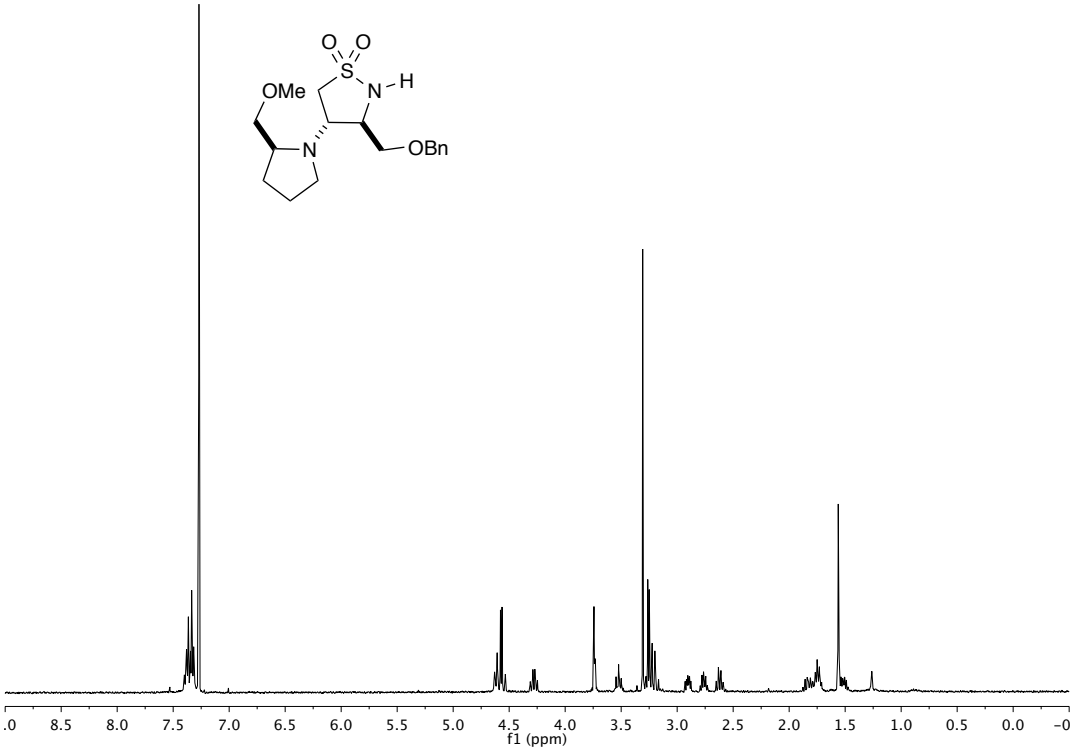


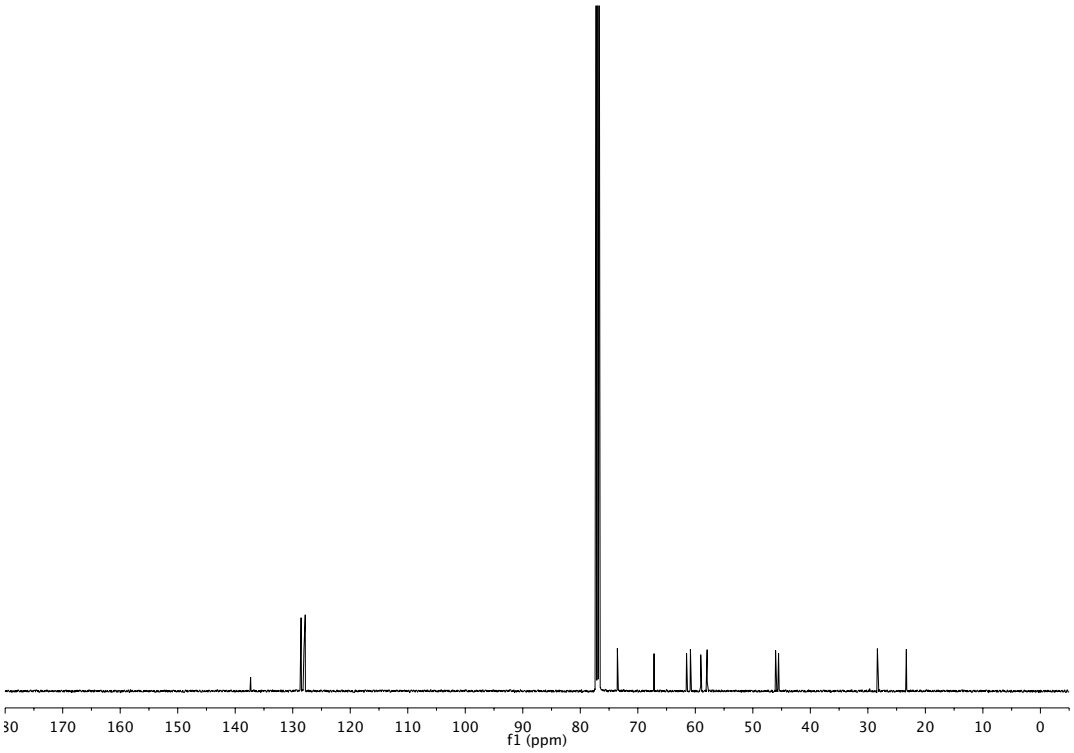
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*S*)-2-(hydroxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.18)



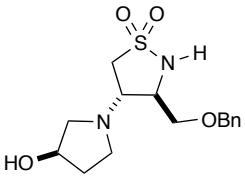


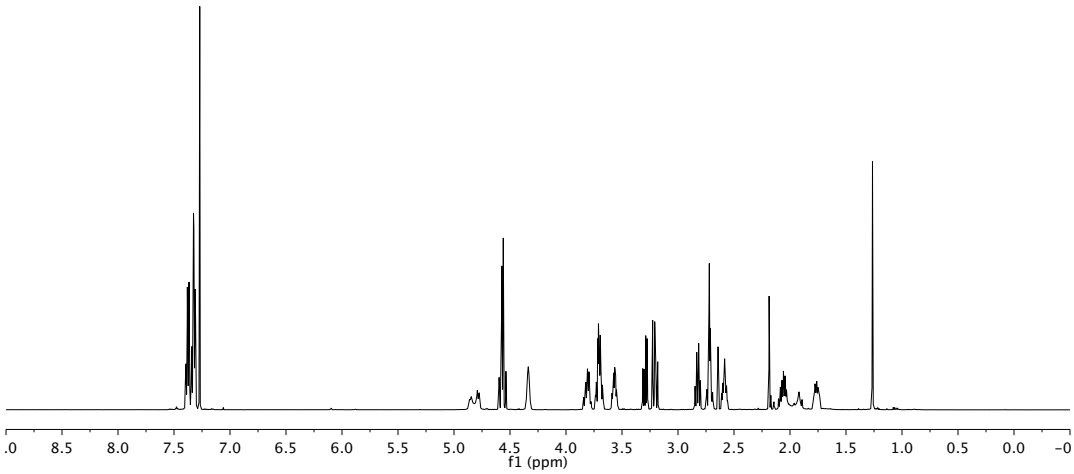
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*S*)-2-(methoxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.19)

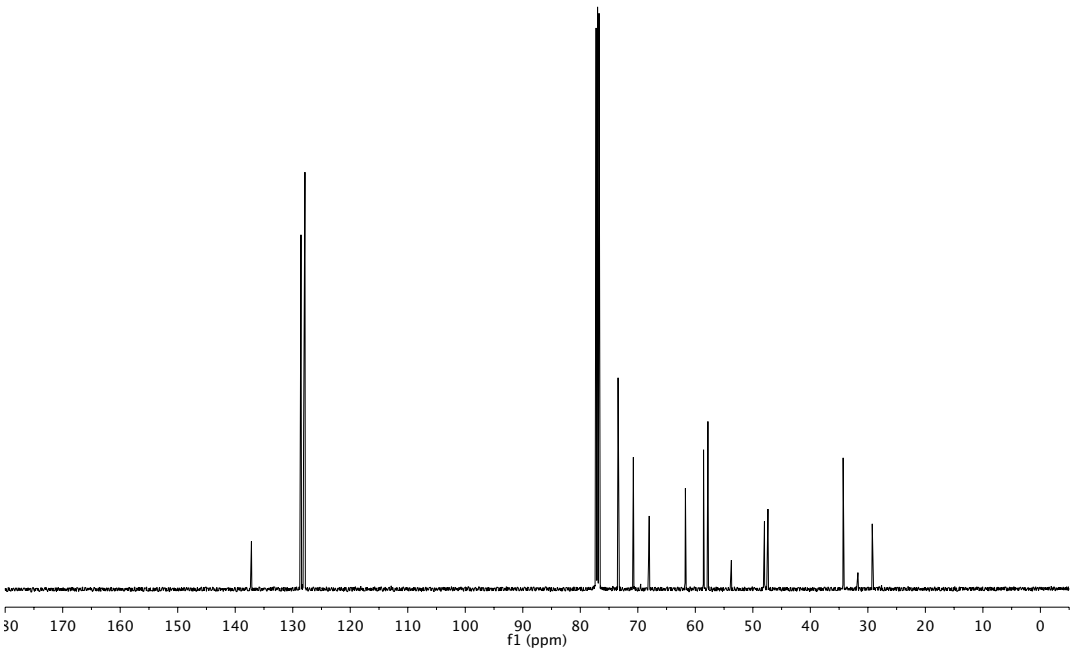




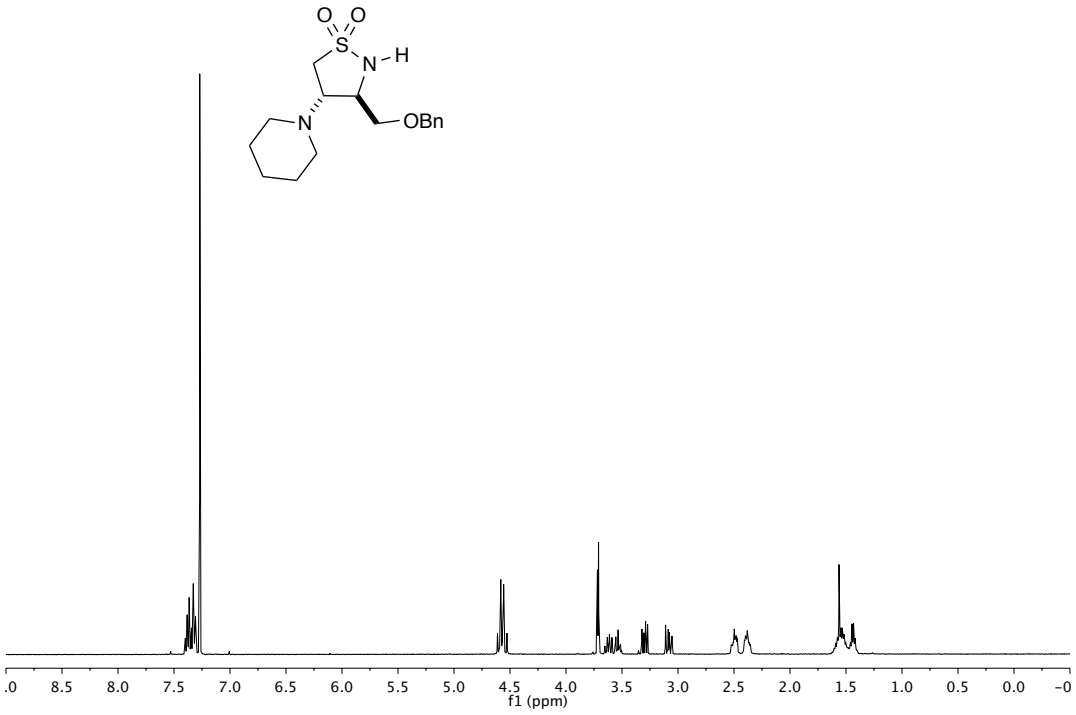
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*R*)-3-hydroxypyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.20)

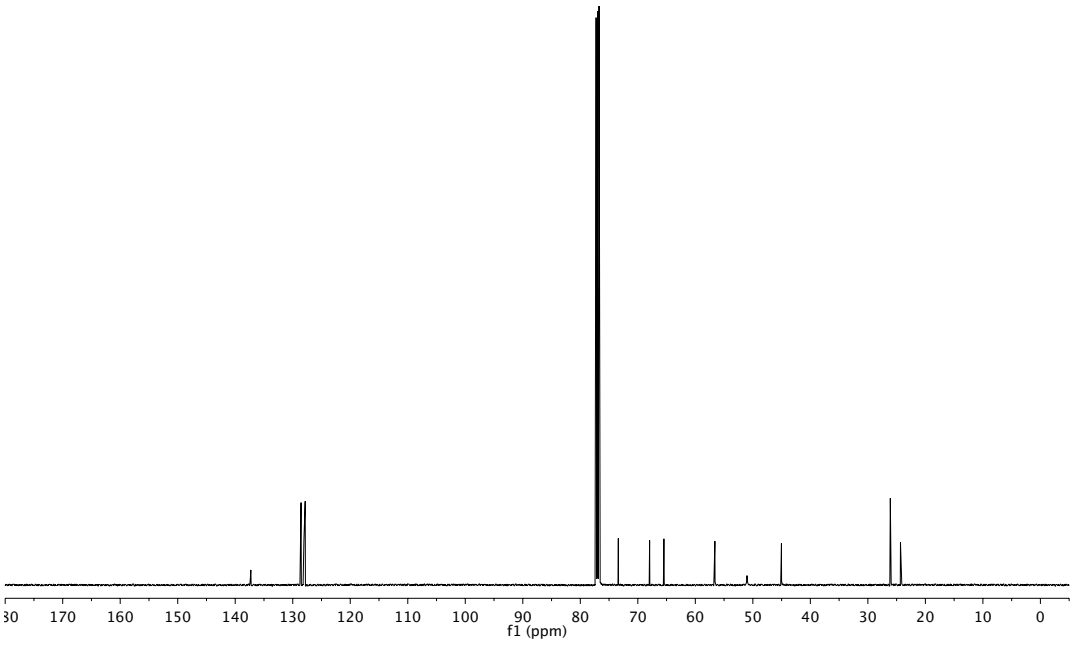




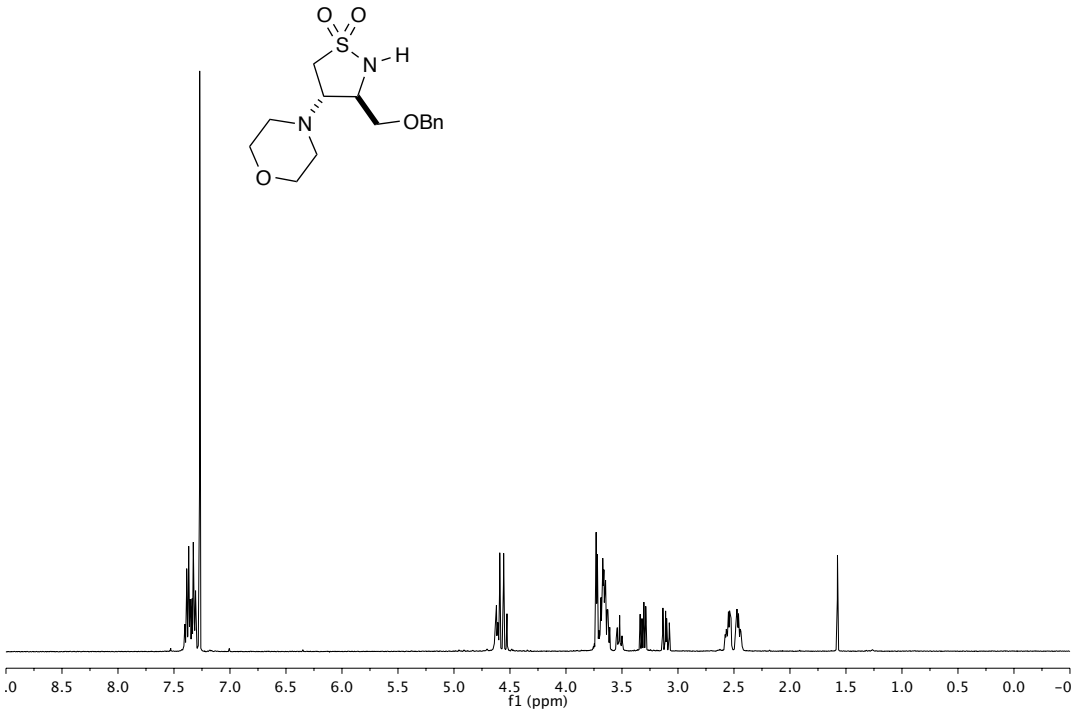


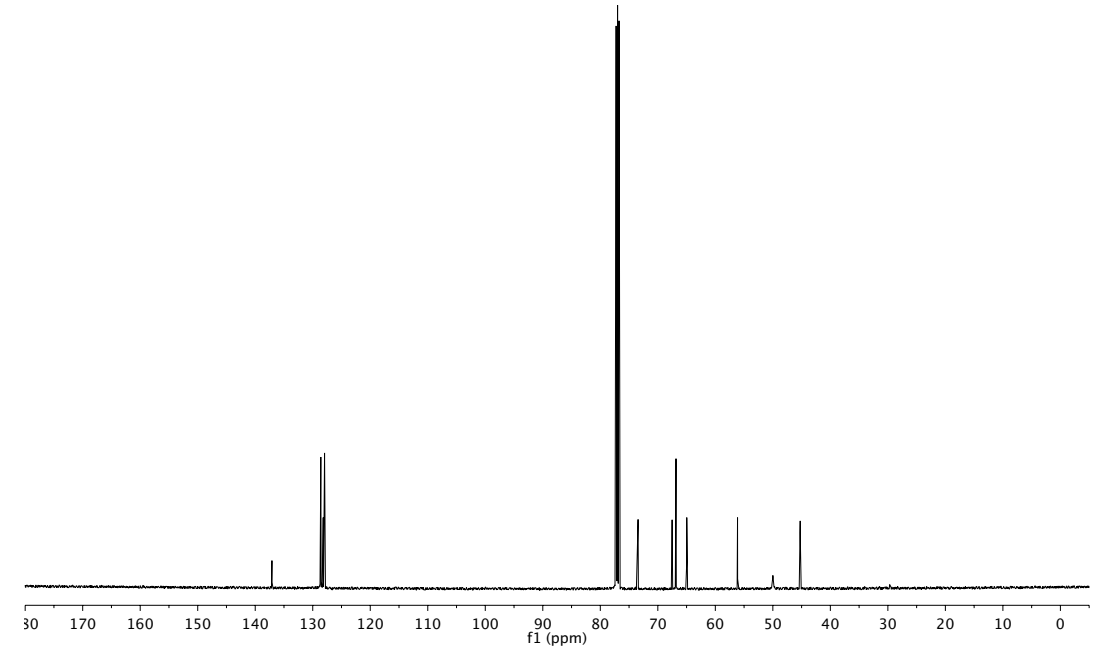
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(piperidin-1-yl)isothiazolidine 1,1-dioxide (3.21)



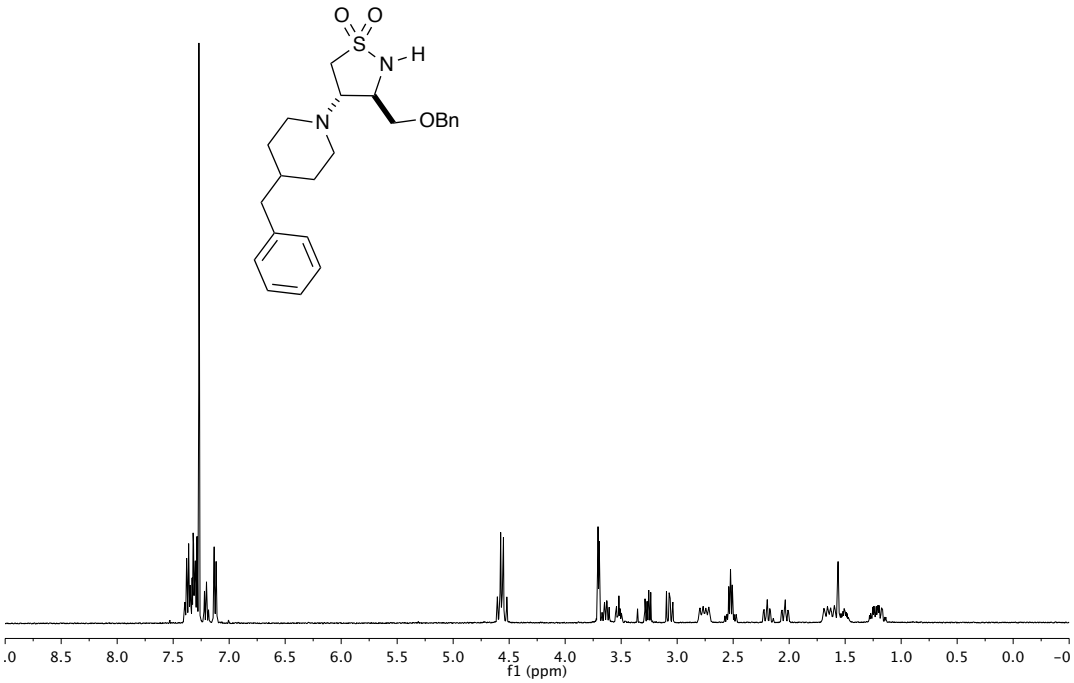


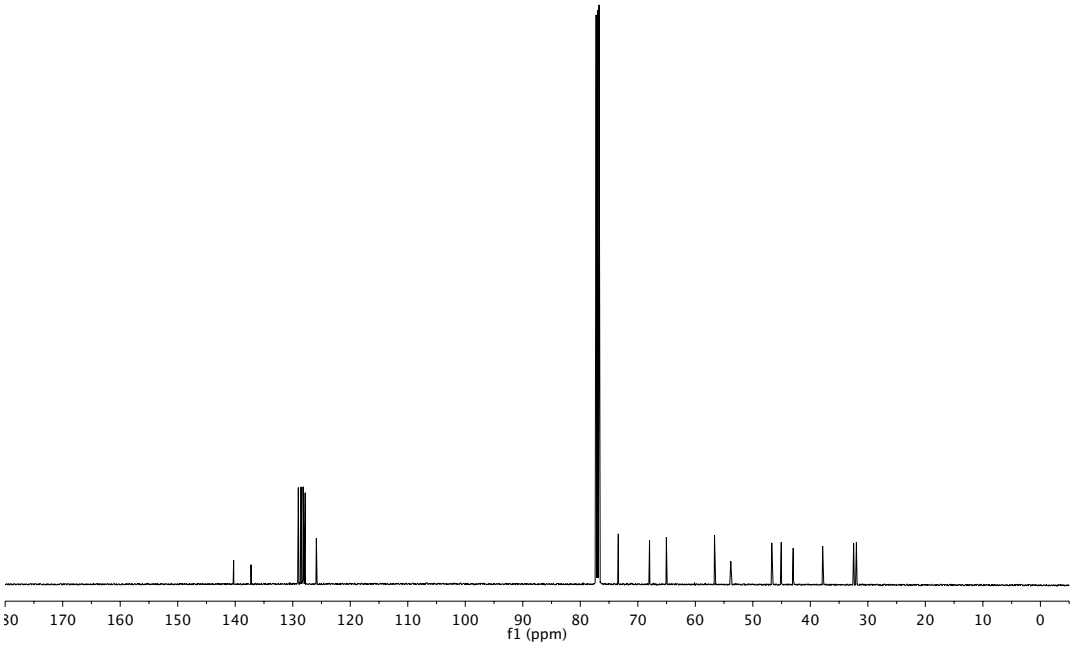
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-morpholinoisothiazolidine 1,1-dioxide (3.22)



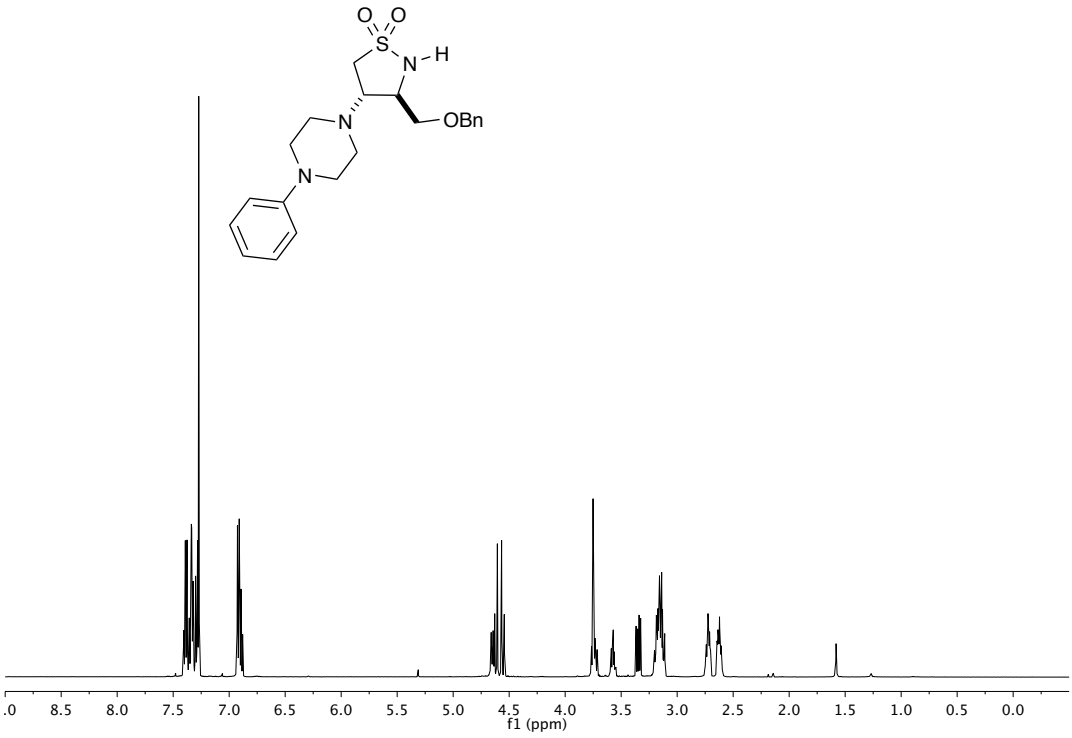


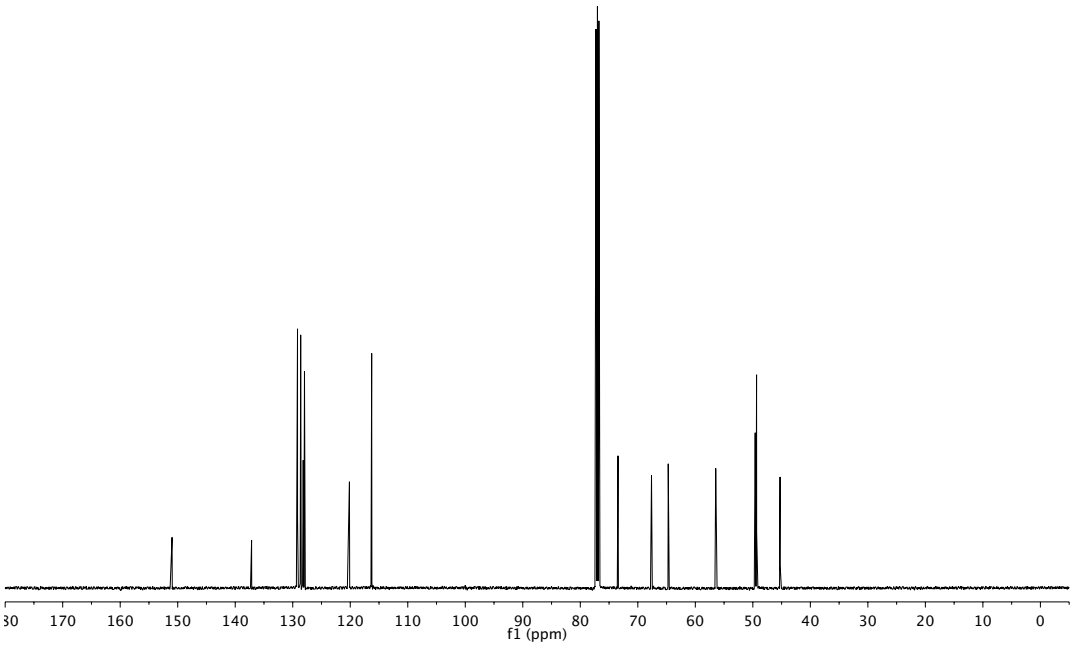
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(4-benzylpiperidin-1-yl)isothiazolidine 1,1-dioxide (3.23)



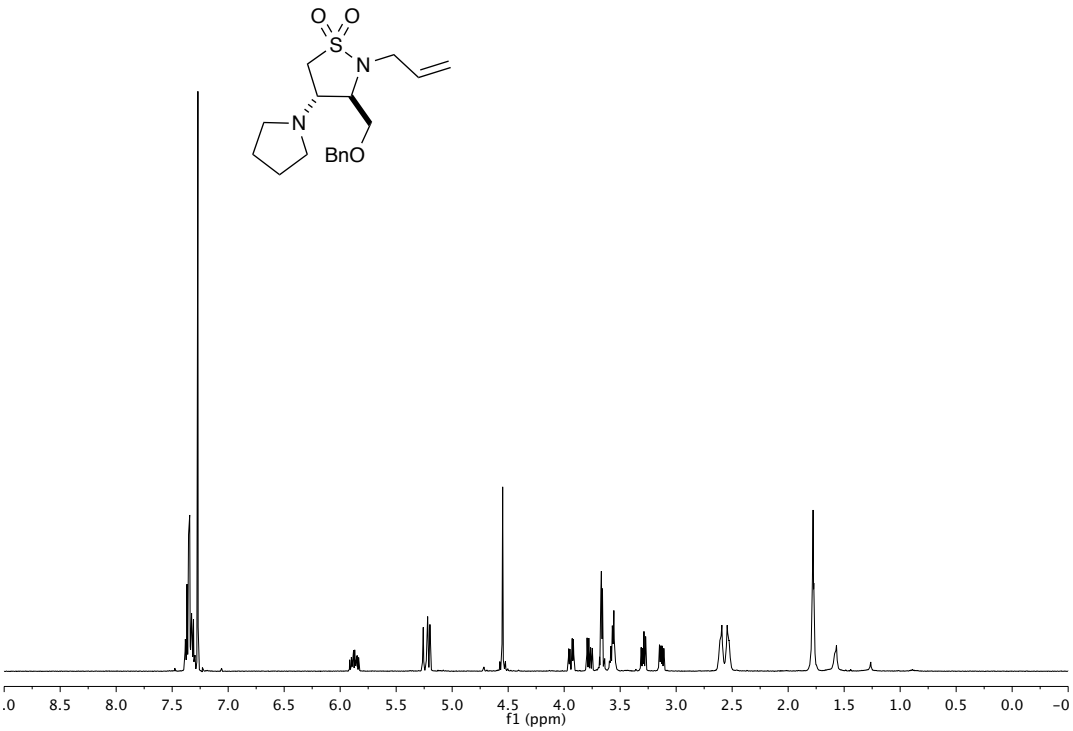


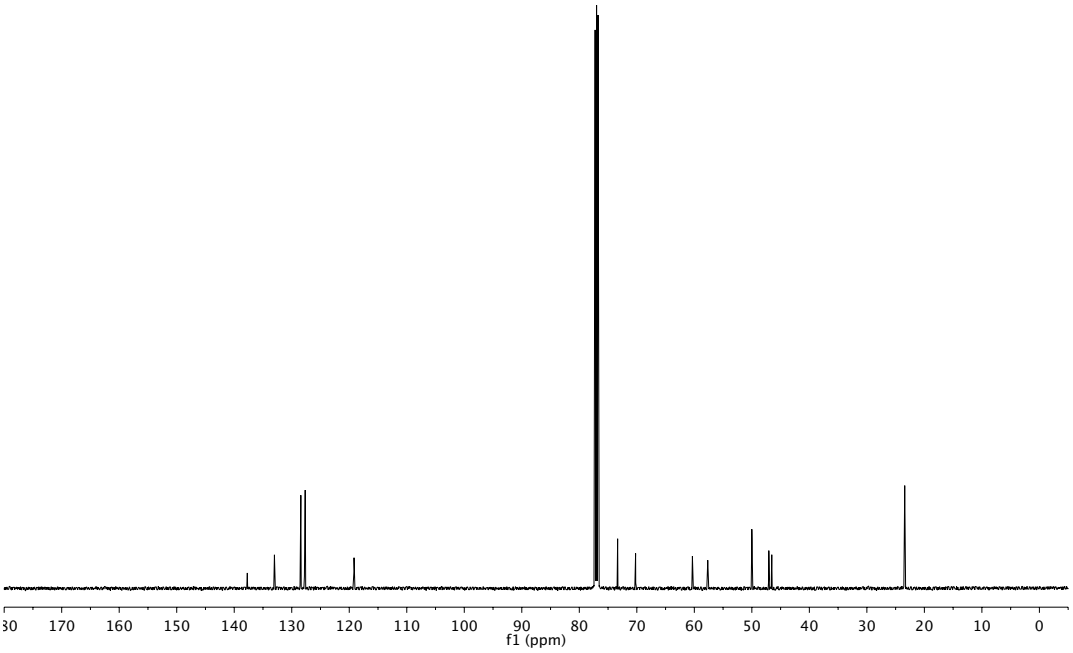
(3*R*,4*S*)-3-((Benzyloxy)methyl)-4-(4-phenylpiperazin-1-yl)isothiazolidine 1,1-dioxide (3.24)



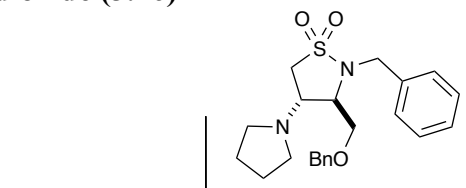


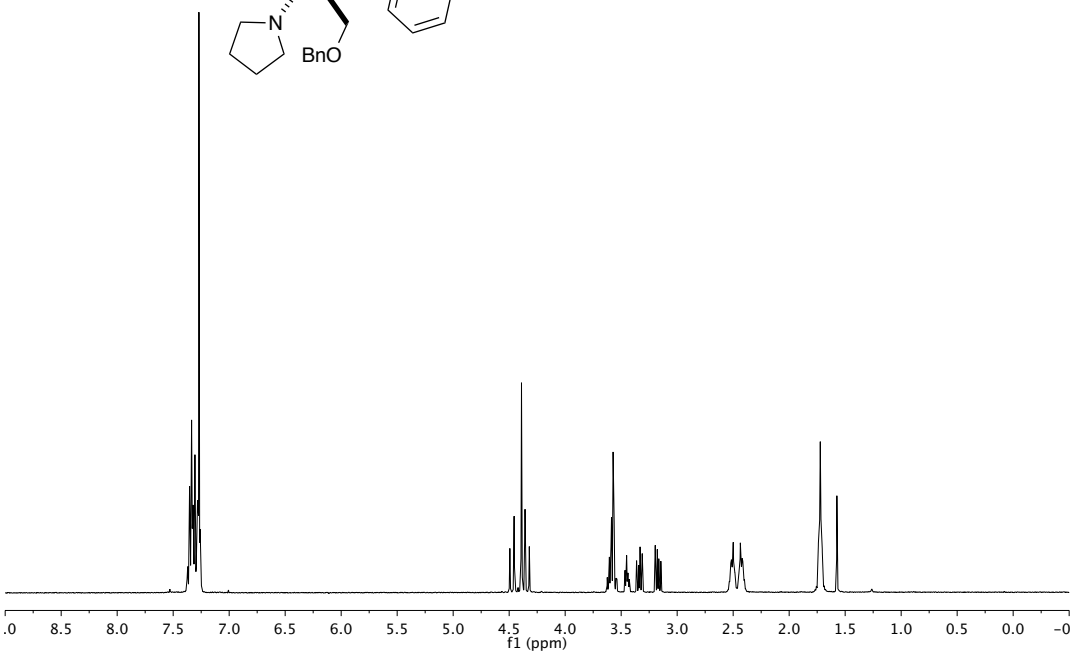
(3*S*,4*R*)-2-Allyl-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.25)

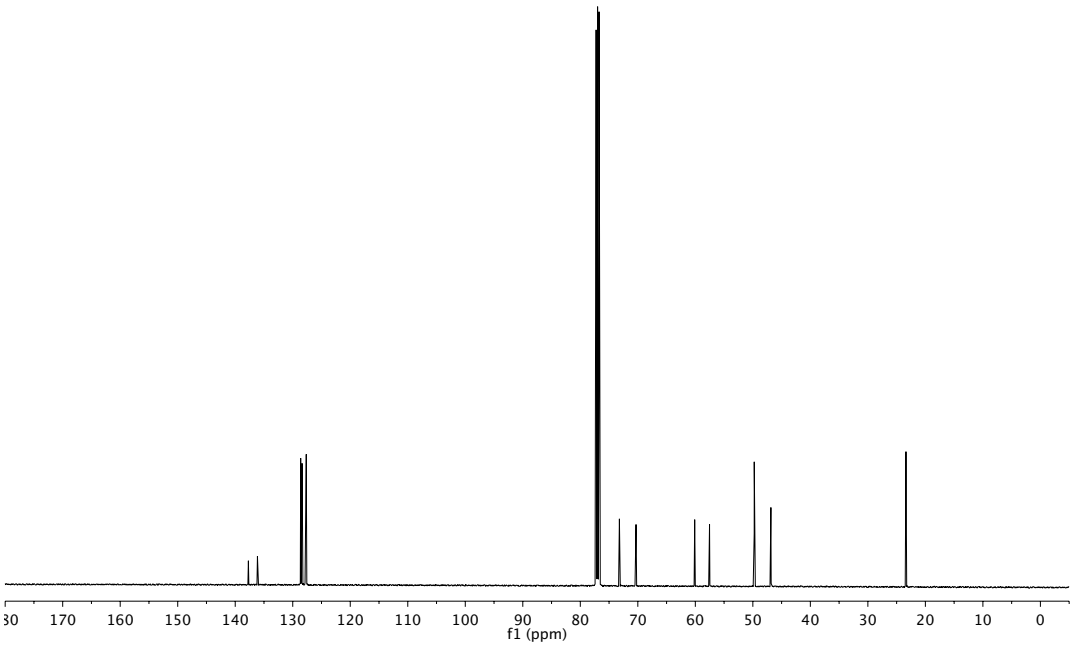




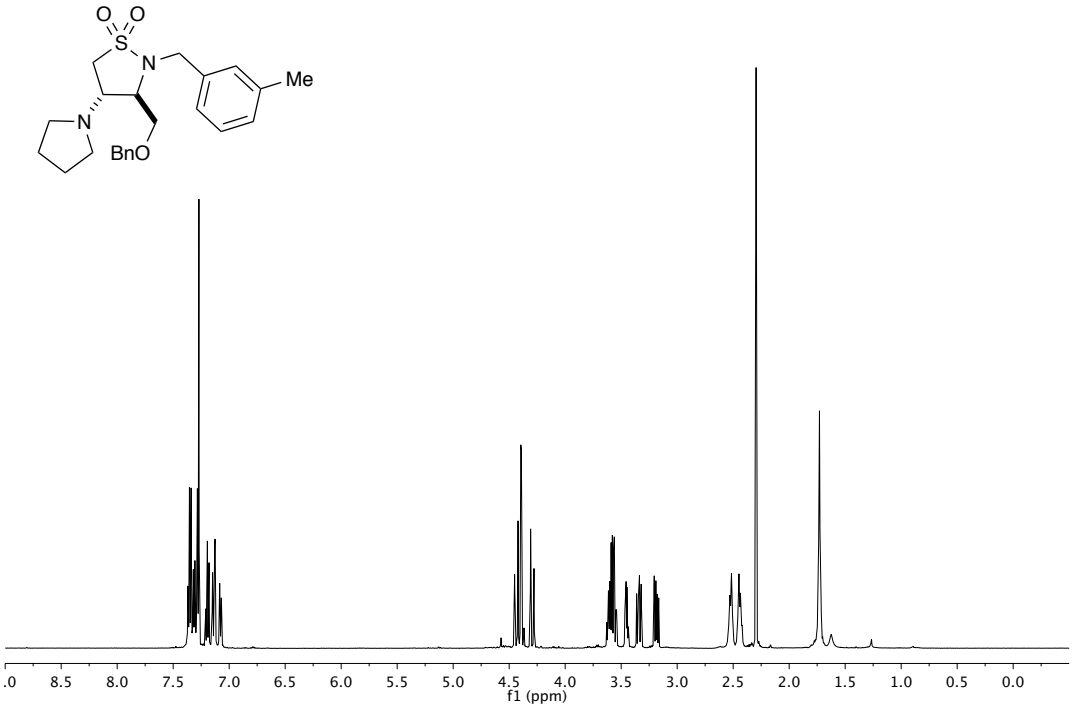
(3*R*,4*S*)-2-Benzyl-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.26)

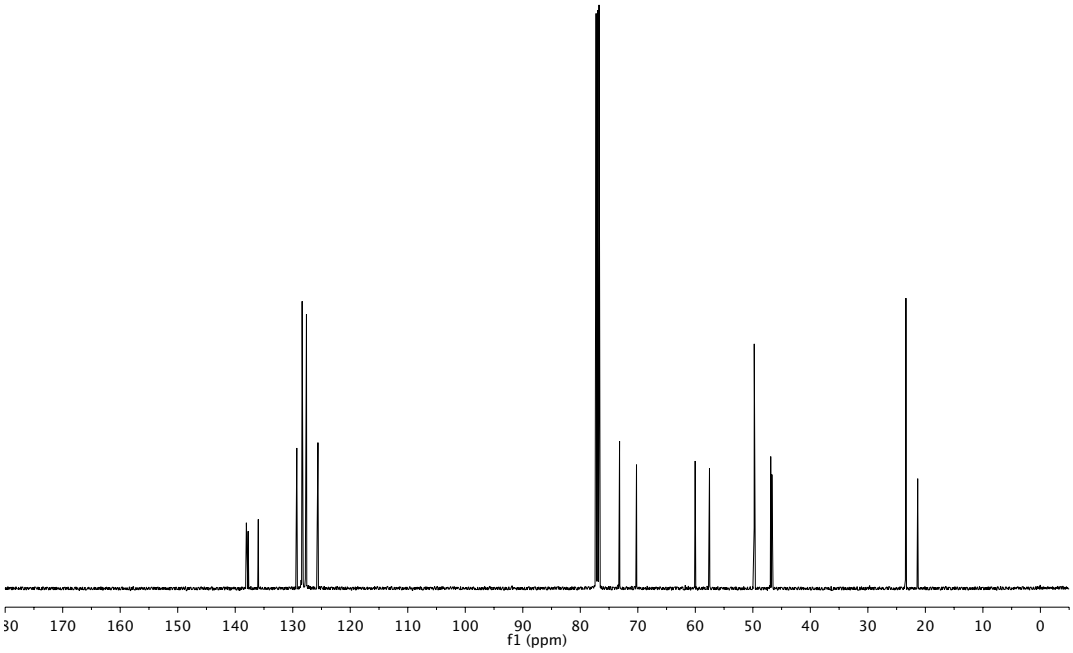




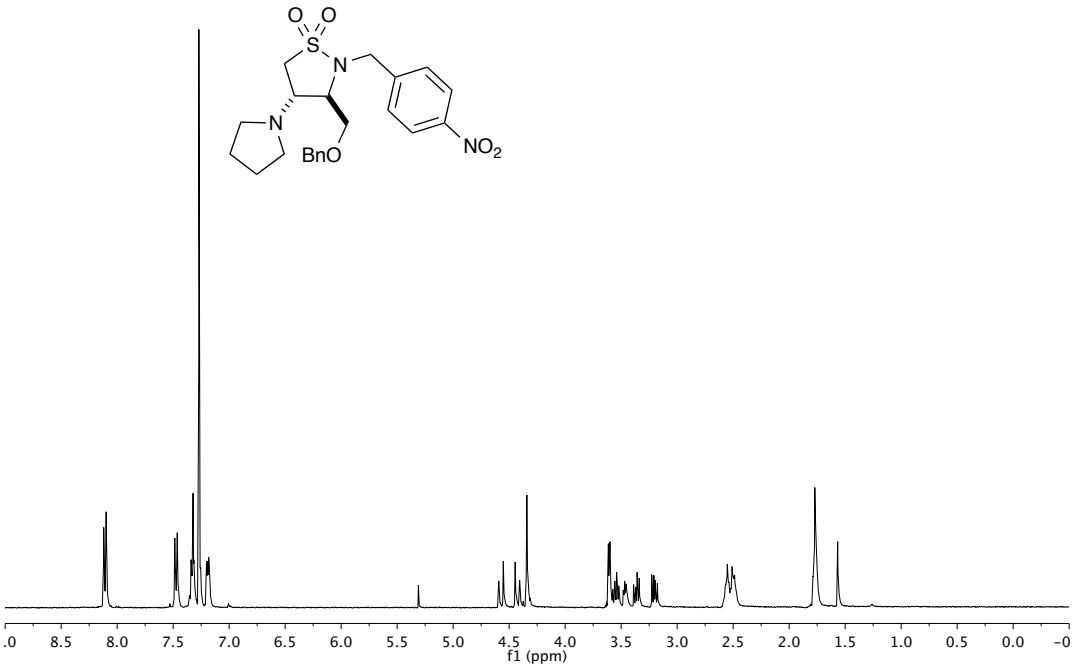


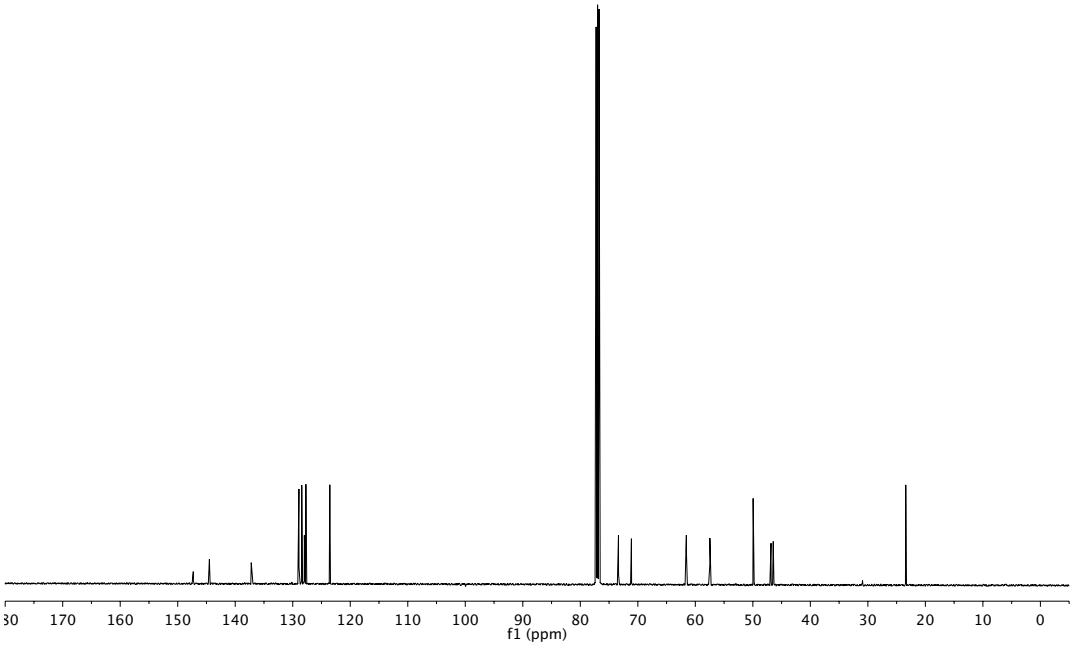
(3*S*,4*R*)-3-((Benzyloxy)methyl)-2-(3-methylbenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.27)



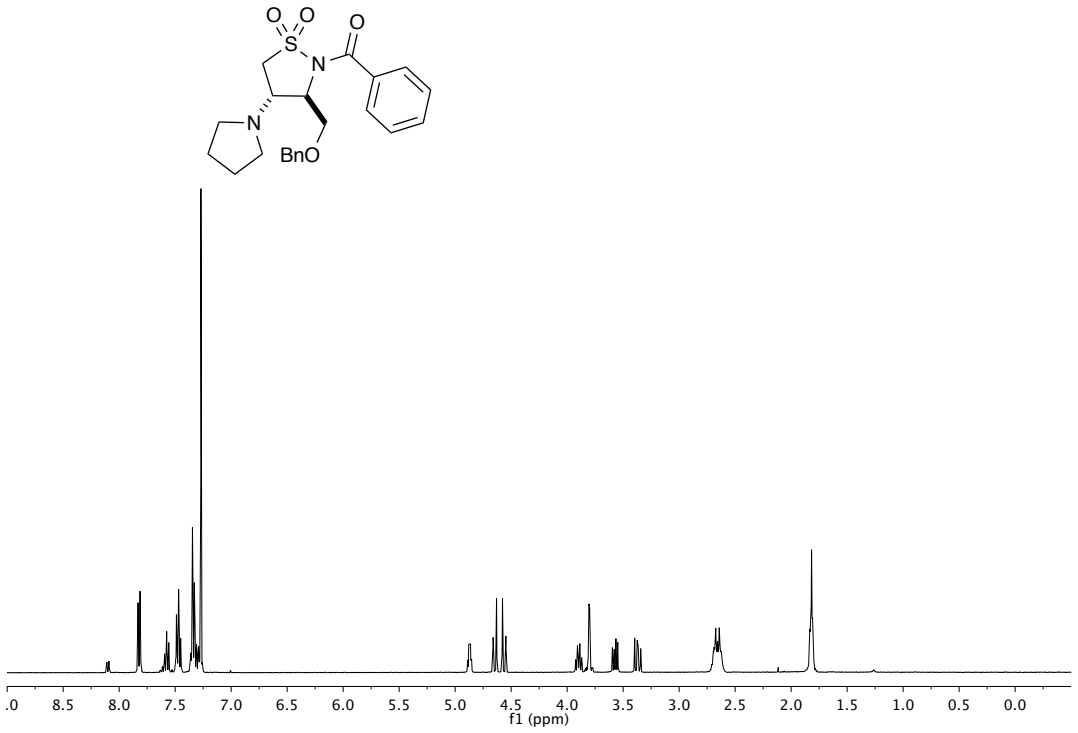


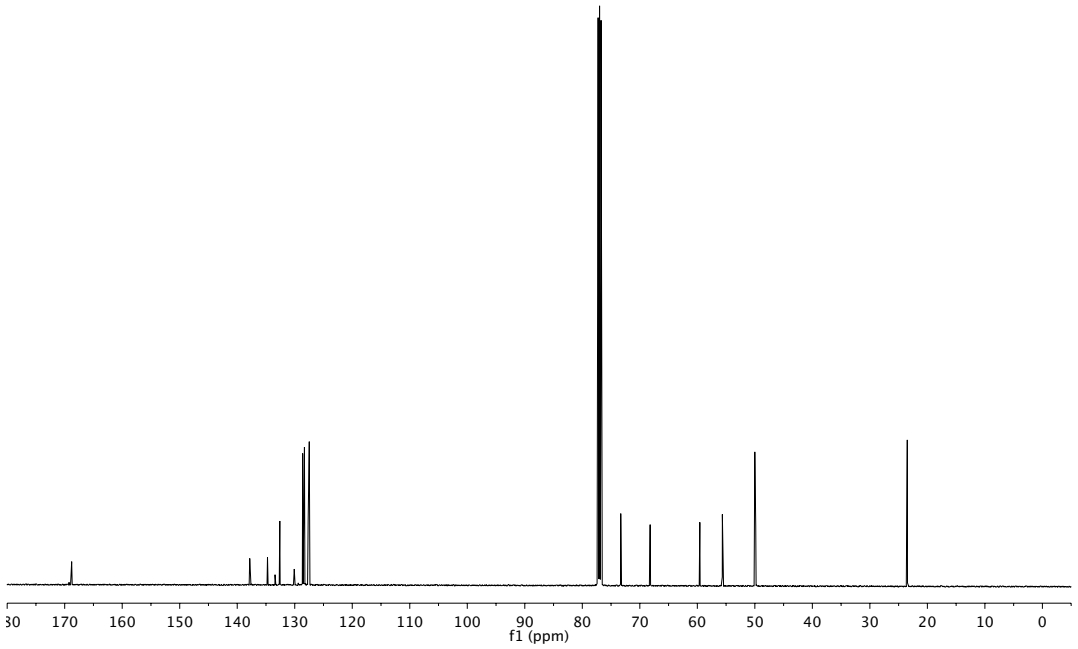
(3*S*,4*R*)-3-((Benzyloxy)methyl)-2-(4-nitrobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.28)



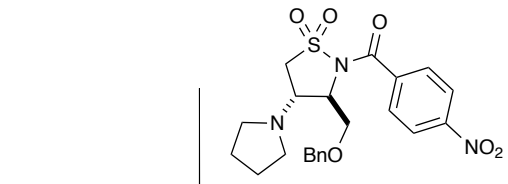


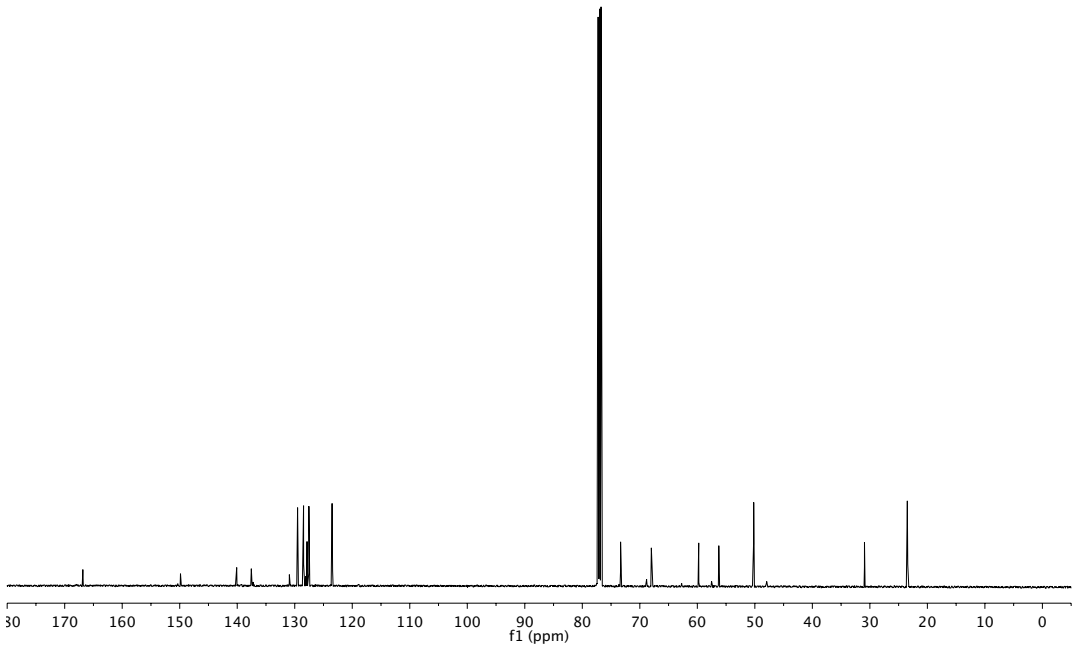
((3*R*,4*S*)-3-((Benzyloxy)methyl)-1,1-dioxido-4-(pyrrolidin-1-yl)isothiazolidin-2-yl)(phenyl)methanone (3.29)



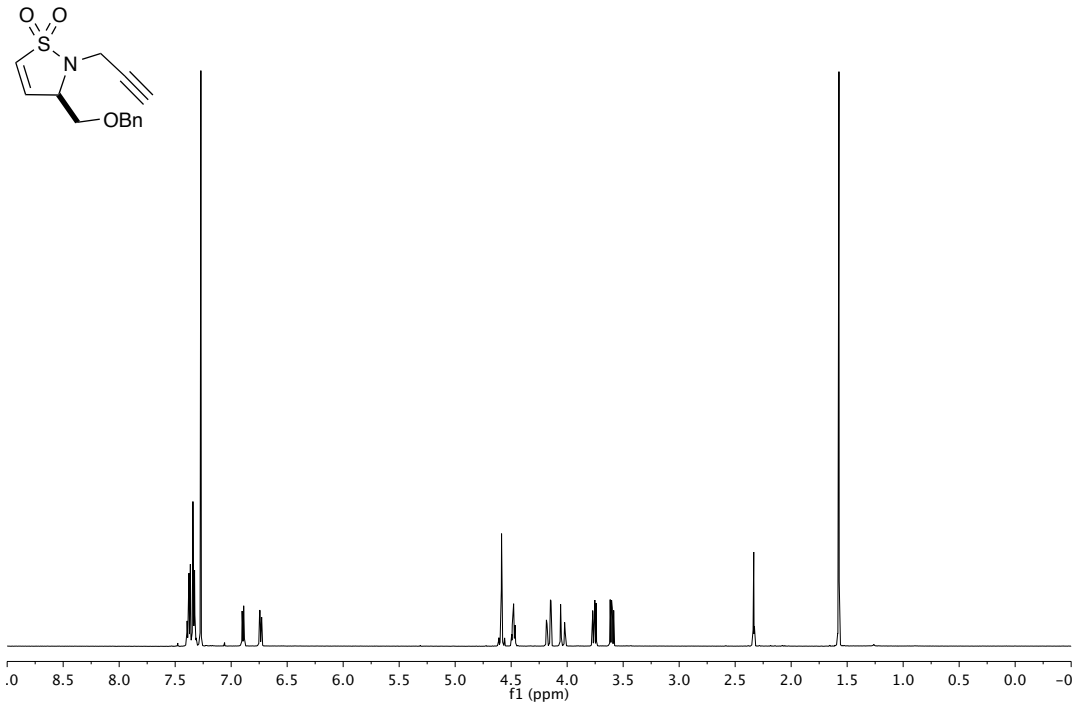


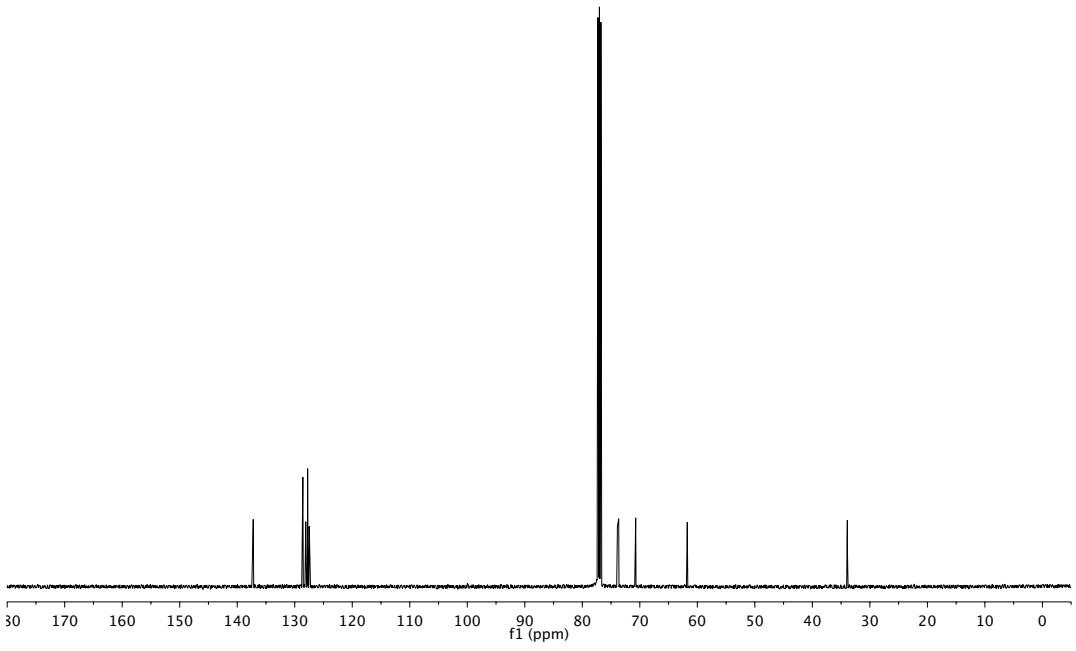
(*R*)-(3-((Benzyloxy)methyl)-1,1-dioxidoisothiazol-2(3*H*)-yl)(4-nitrophenyl)methanone (3.30)



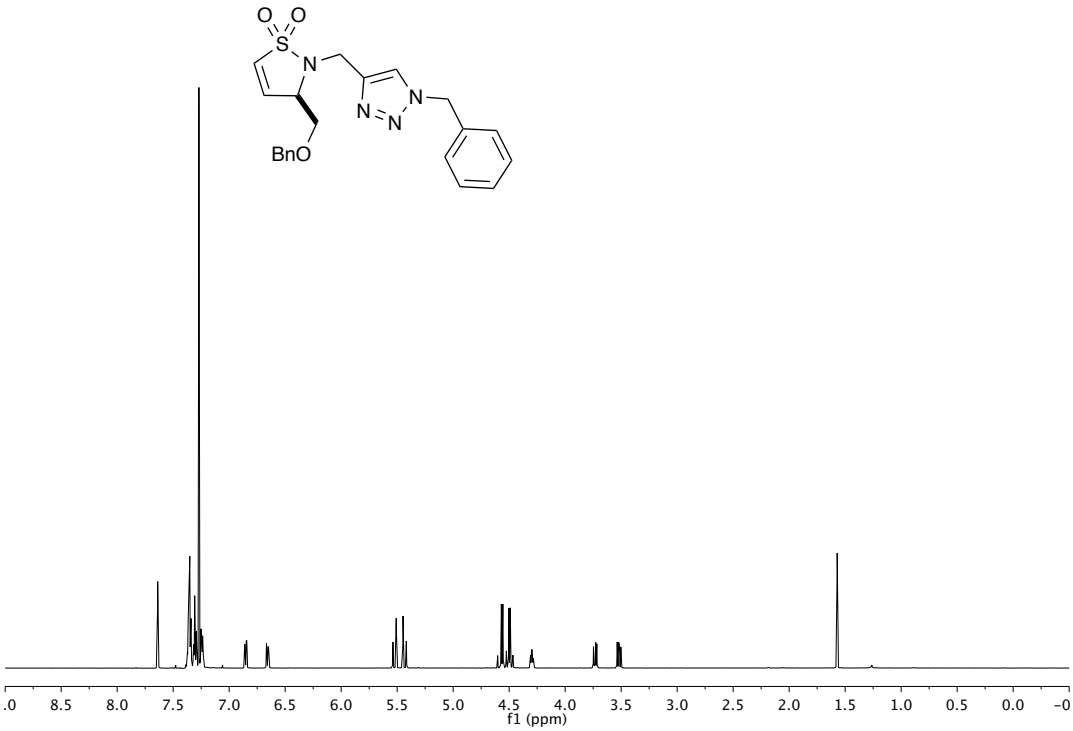


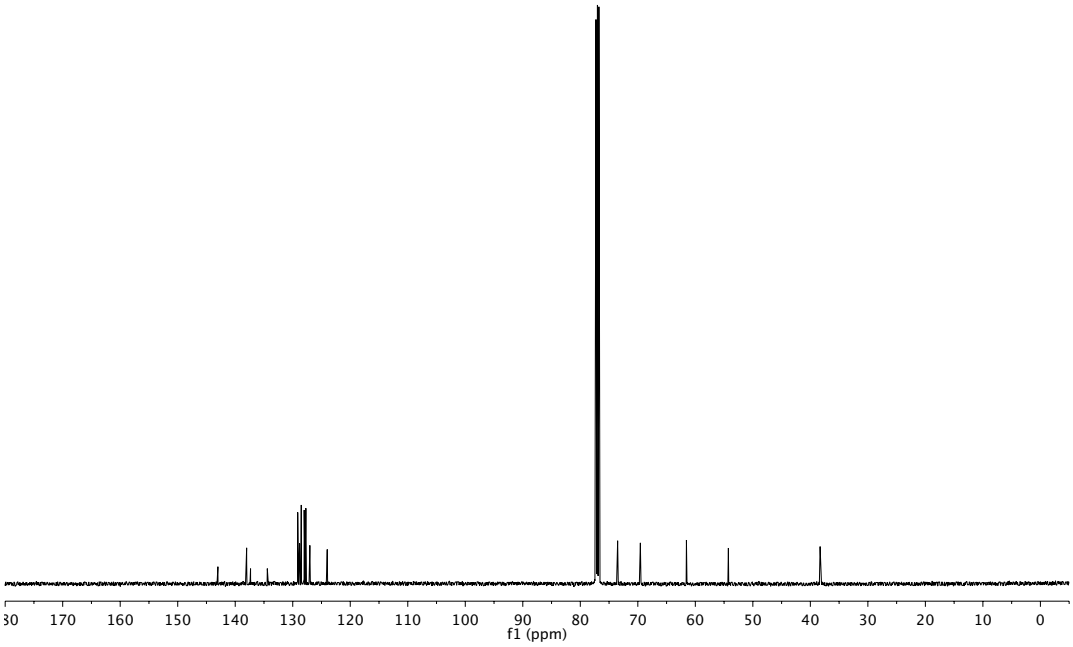
(*R*)-3-((Benzyloxy)methyl)-2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (3.31)



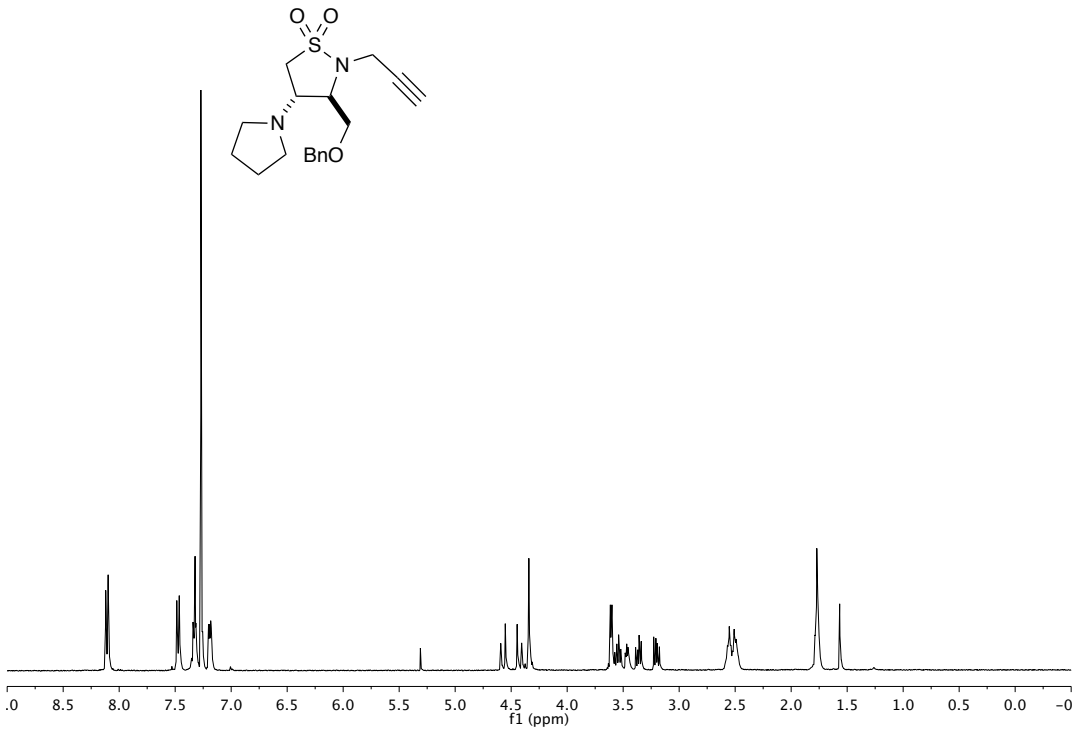


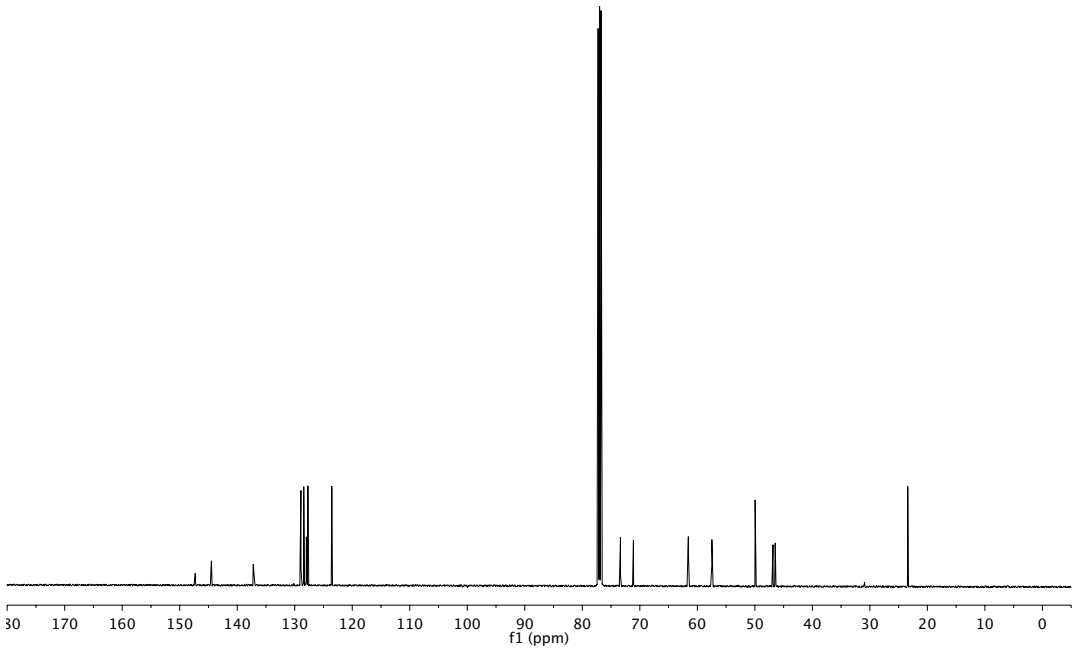
(*R*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-((benzyloxy)methyl)-2,3-dihydroisothiazole 1,1-dioxide (3.32)



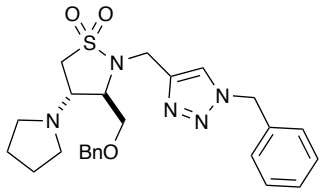


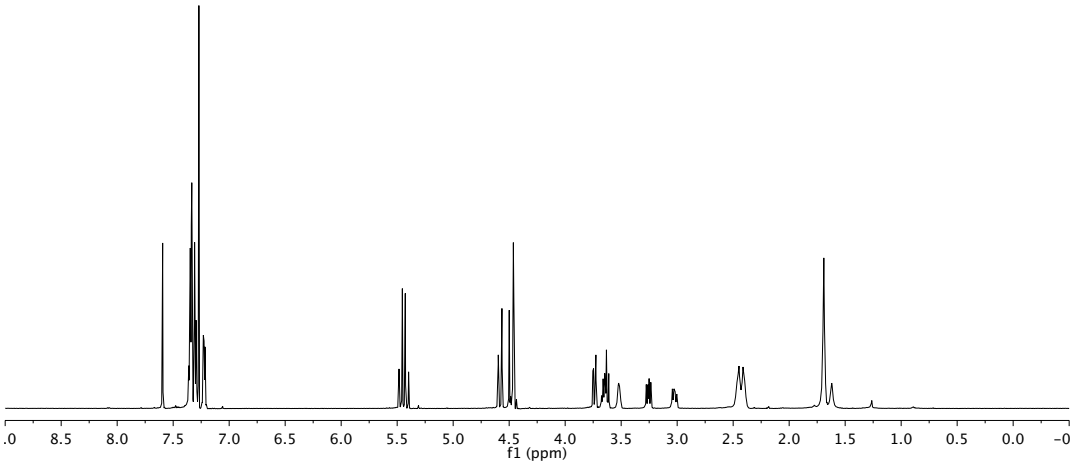
(3*R*,4*S*)-3-((Benzyloxy)methyl)-2-(prop-2-yn-1-yl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.33)

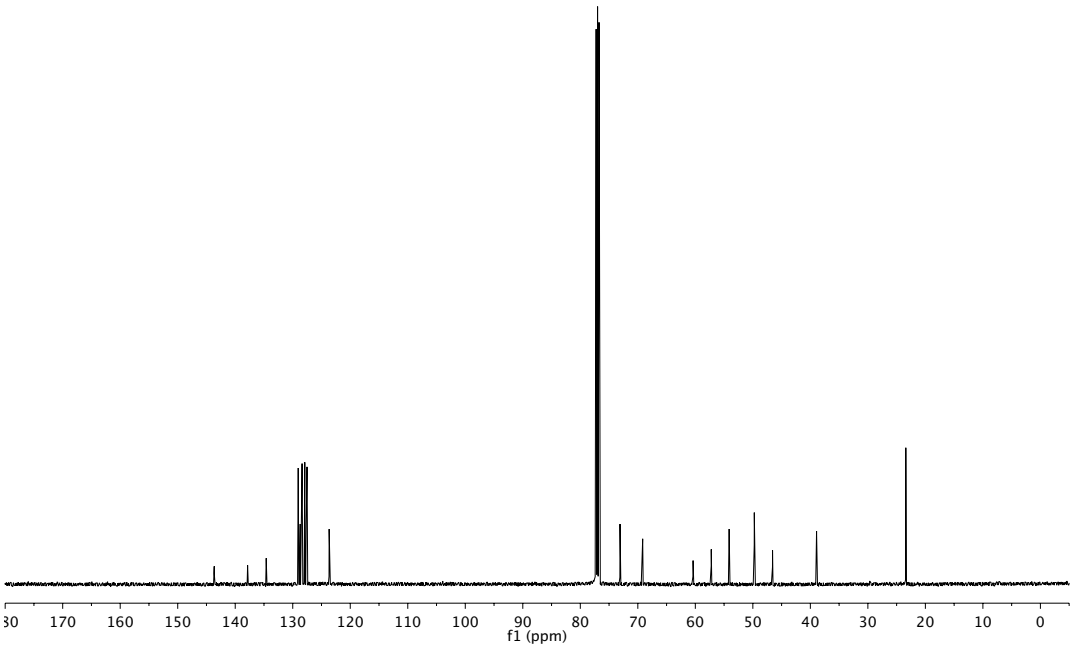




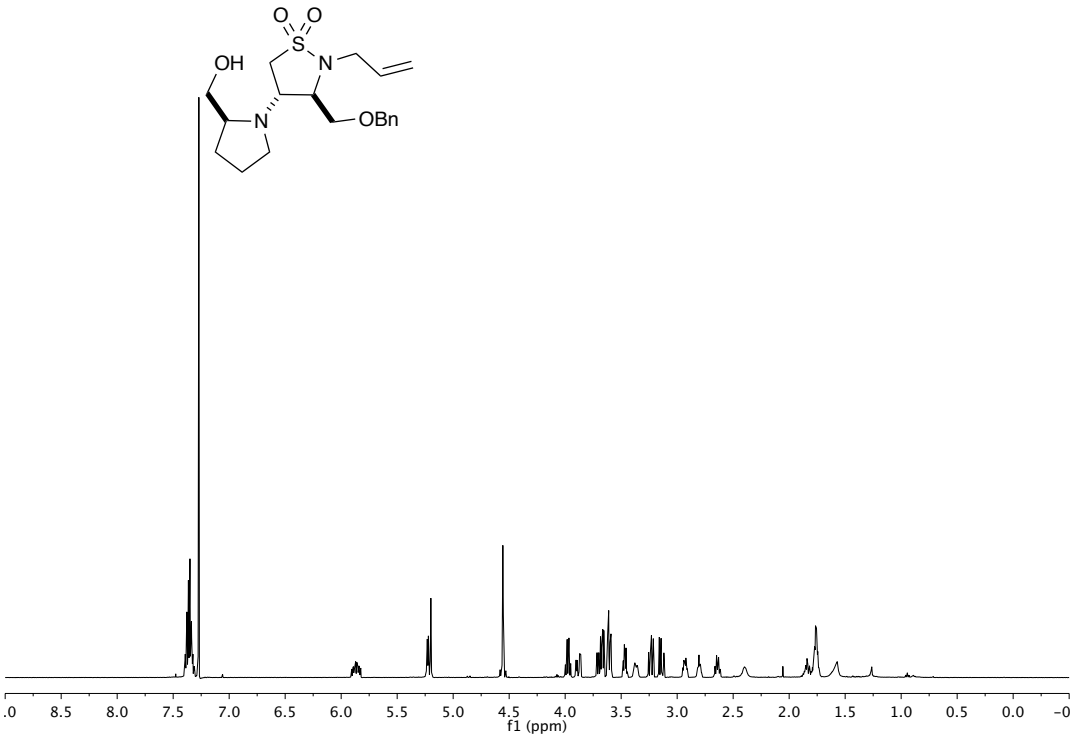
(3*R*,4*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-((benzyloxy)methyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.34)

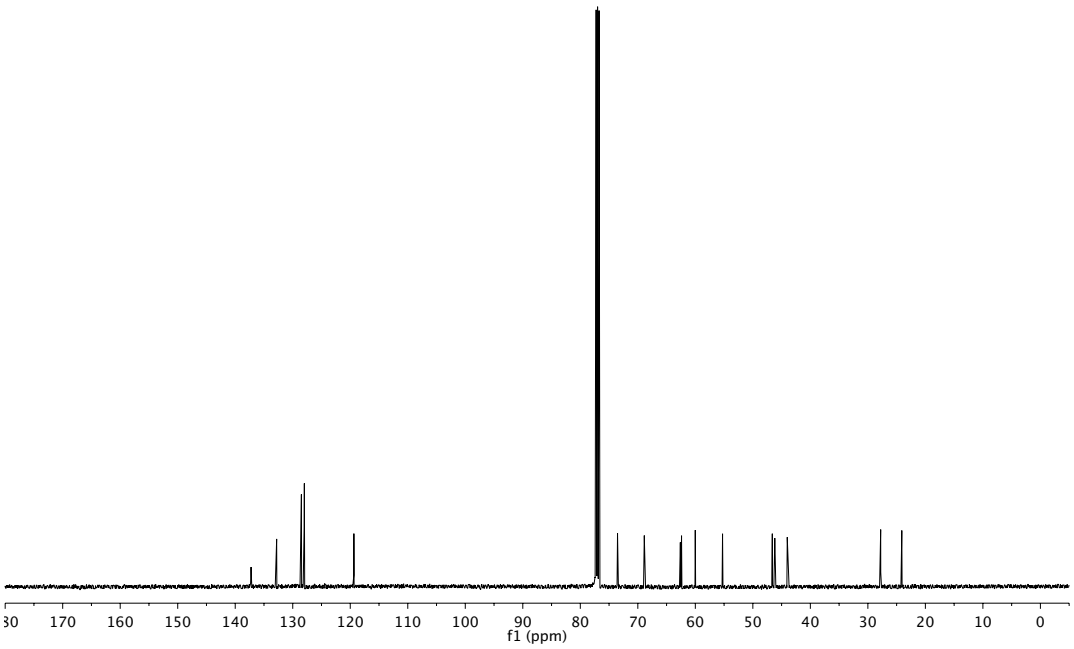




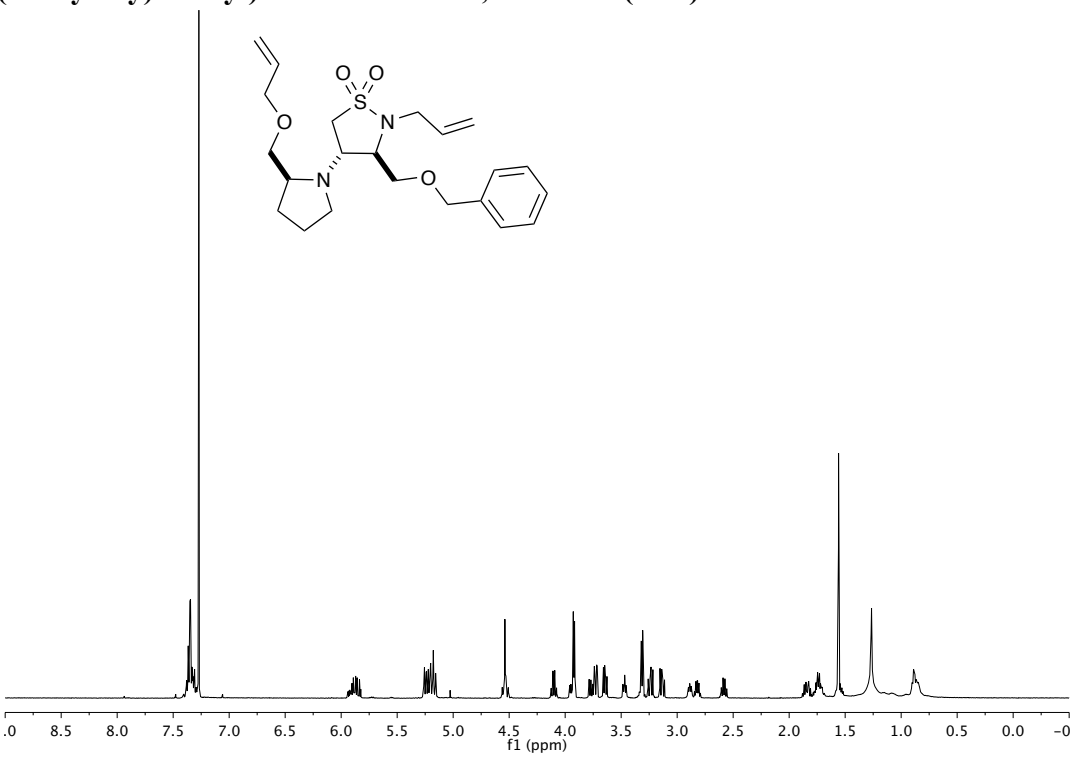


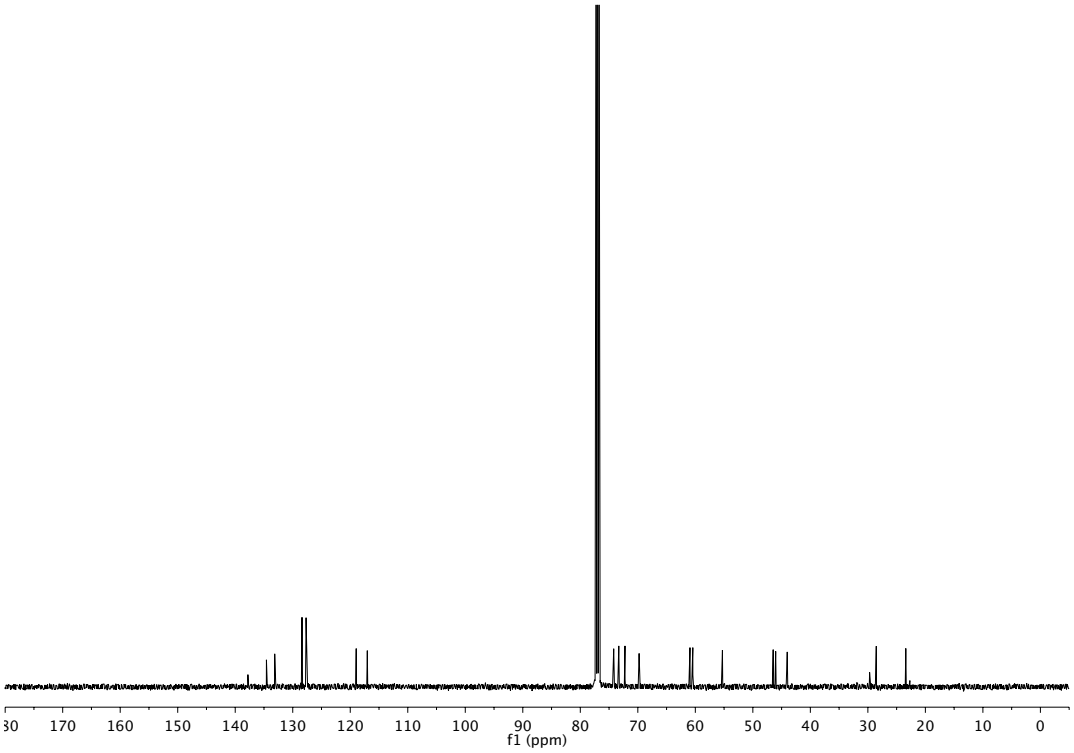
(3*R*,4*S*)-2-Allyl-3-((benzyloxy)methyl)-4-((*S*)-2-(hydroxymethyl)pyrrolidin-1-yl)isothiazolidine 1,1-dioxide (3.35)



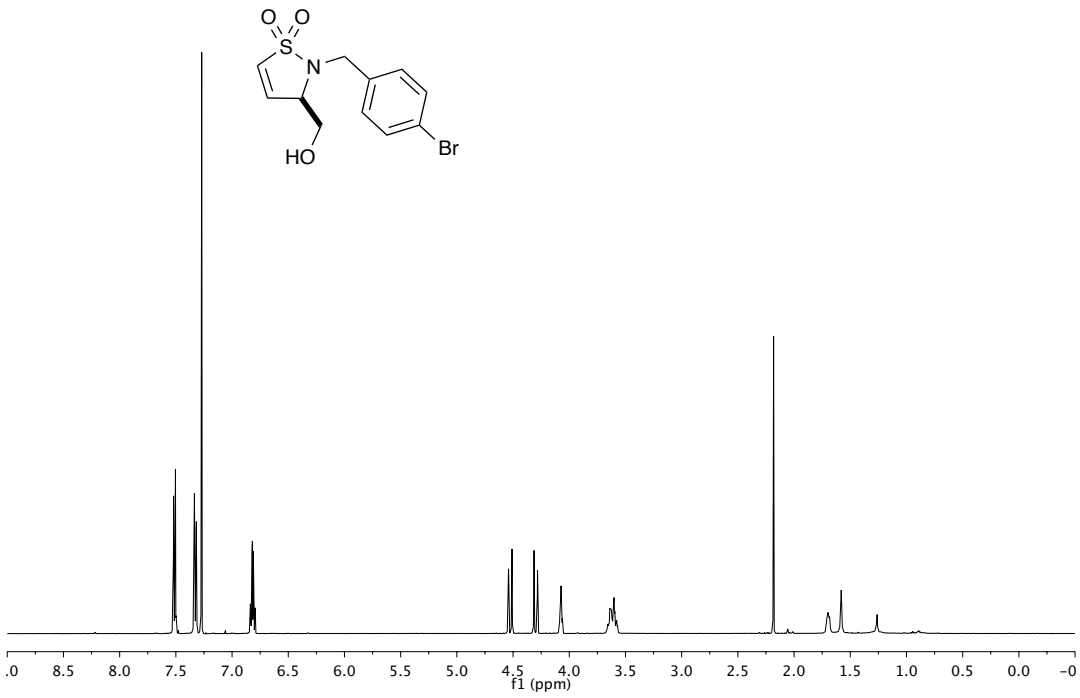


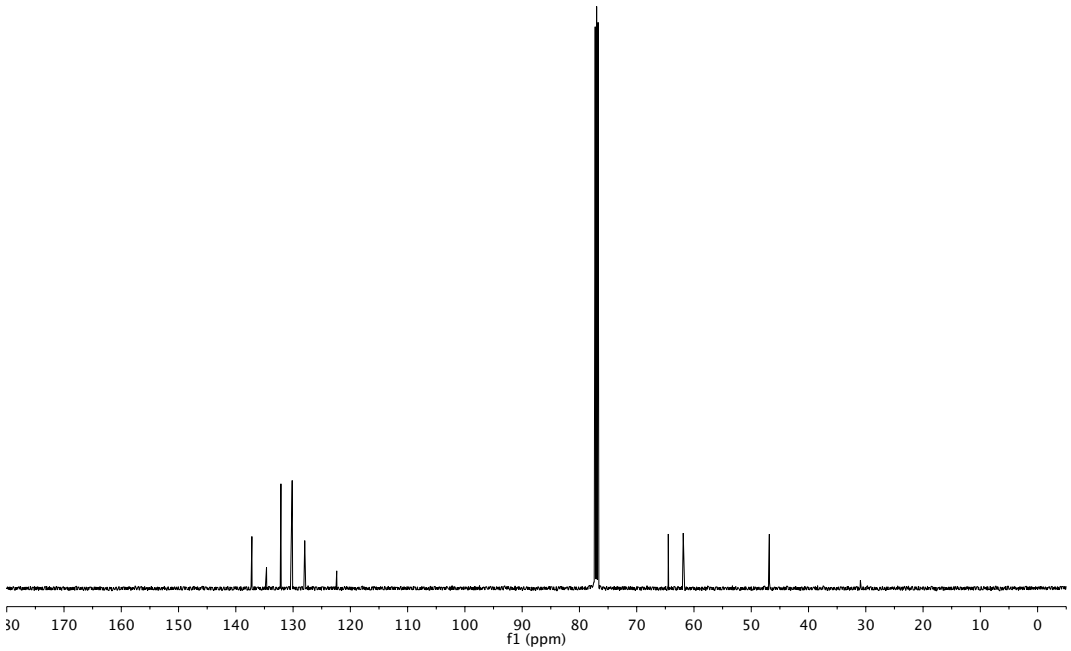
(3*R*,4*S*)-2-Allyl-4-((*S*)-2-((allyloxy)methyl)pyrrolidin-1-yl)-3-((benzyloxy)methyl)isothiazolidine 1,1-dioxide (3.36)



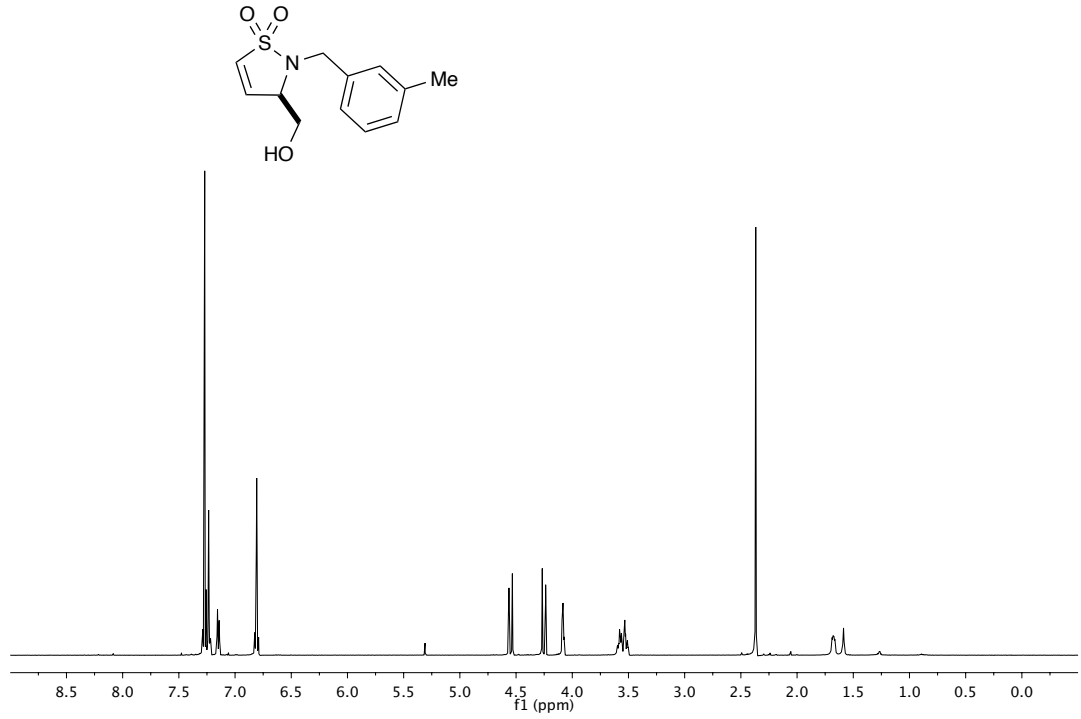


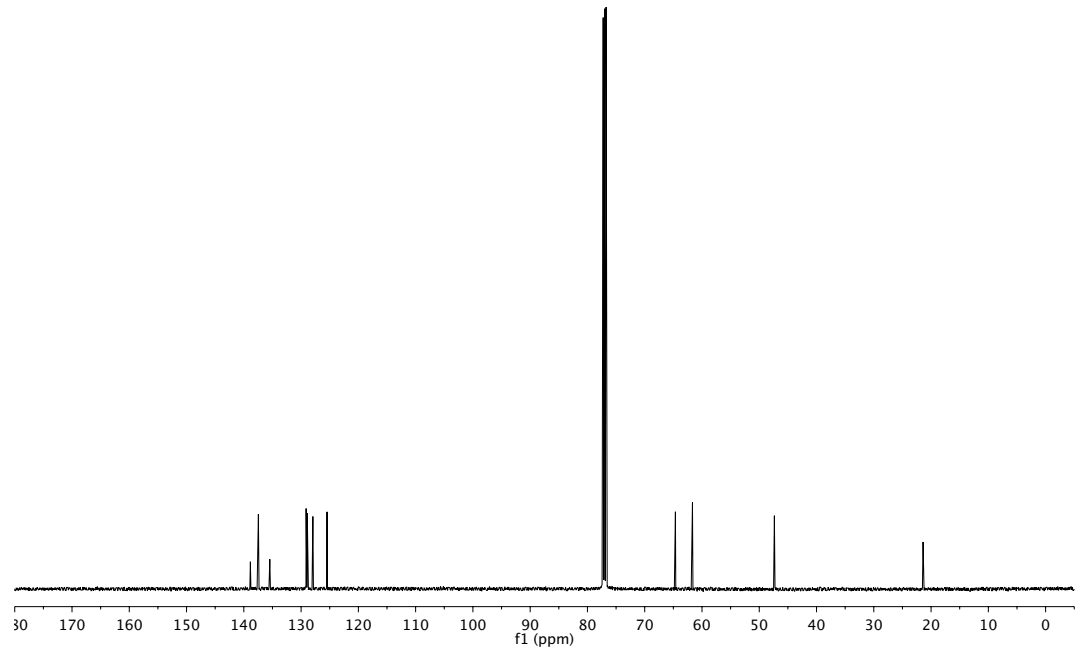
(*R*)-2-(4-Bromobenzyl)-3-(hydroxymethyl)-2,3-dihydroisothiazole 1,1-dioxide (3.37)



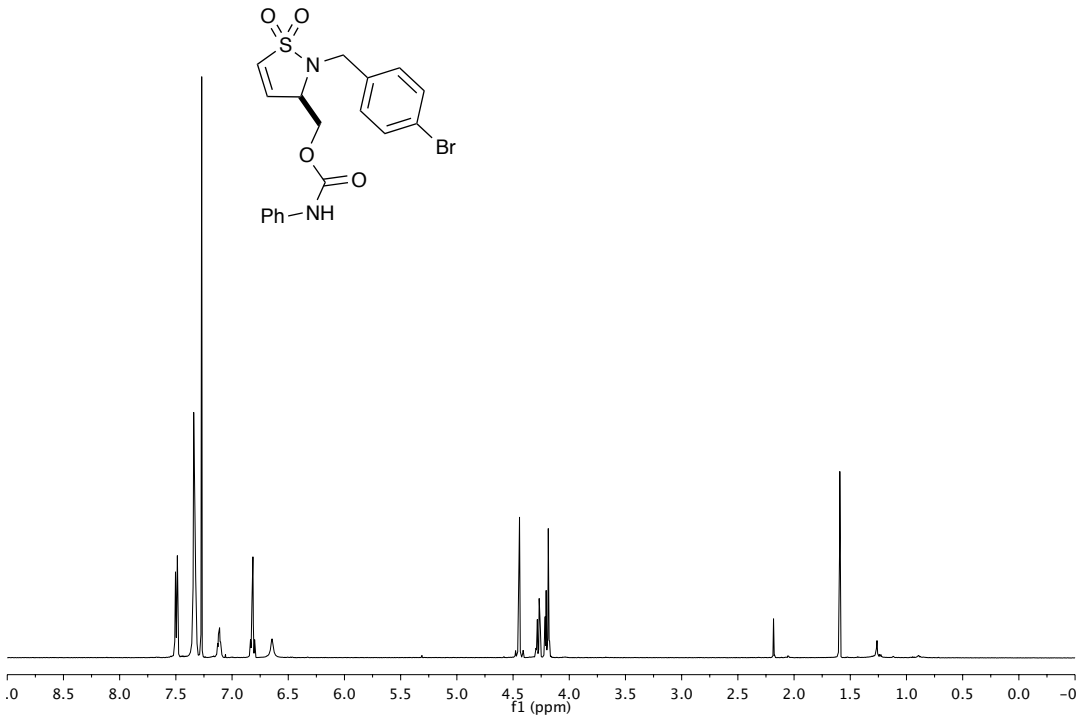


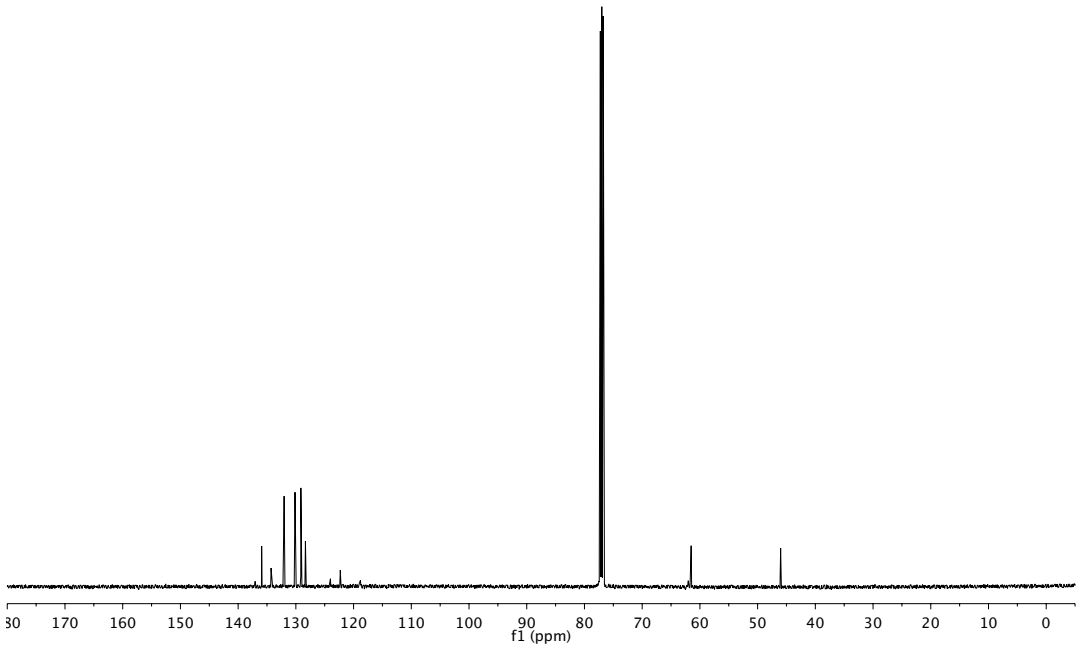
(*R*)-3-(Hydroxymethyl)-2-(3-methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.38)



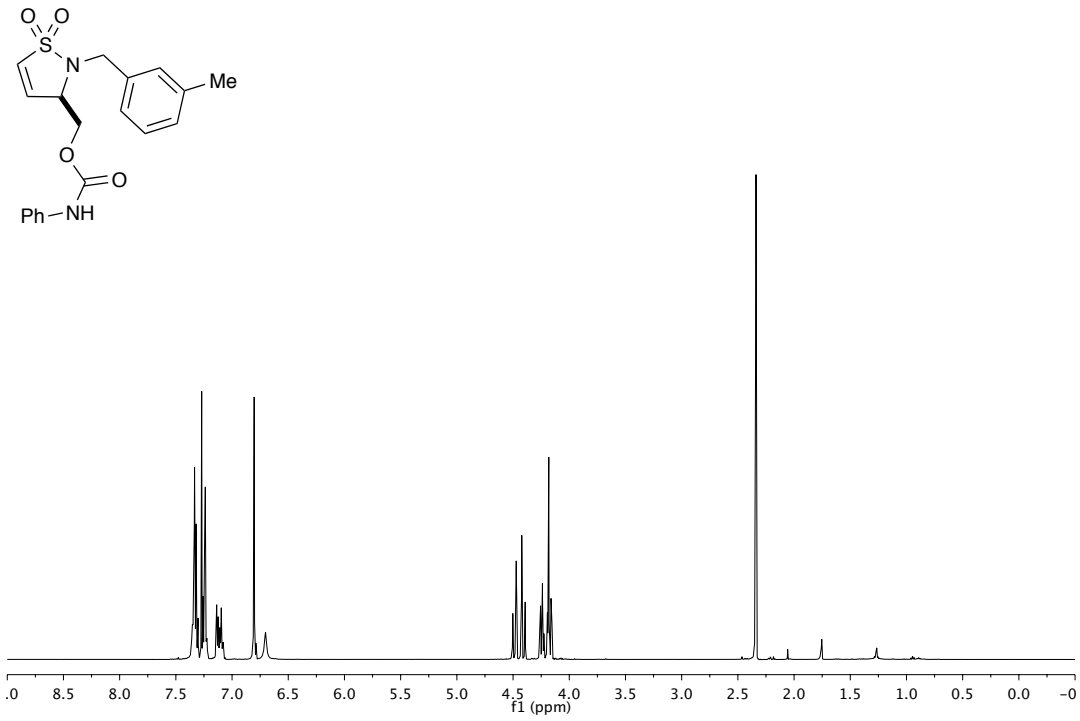


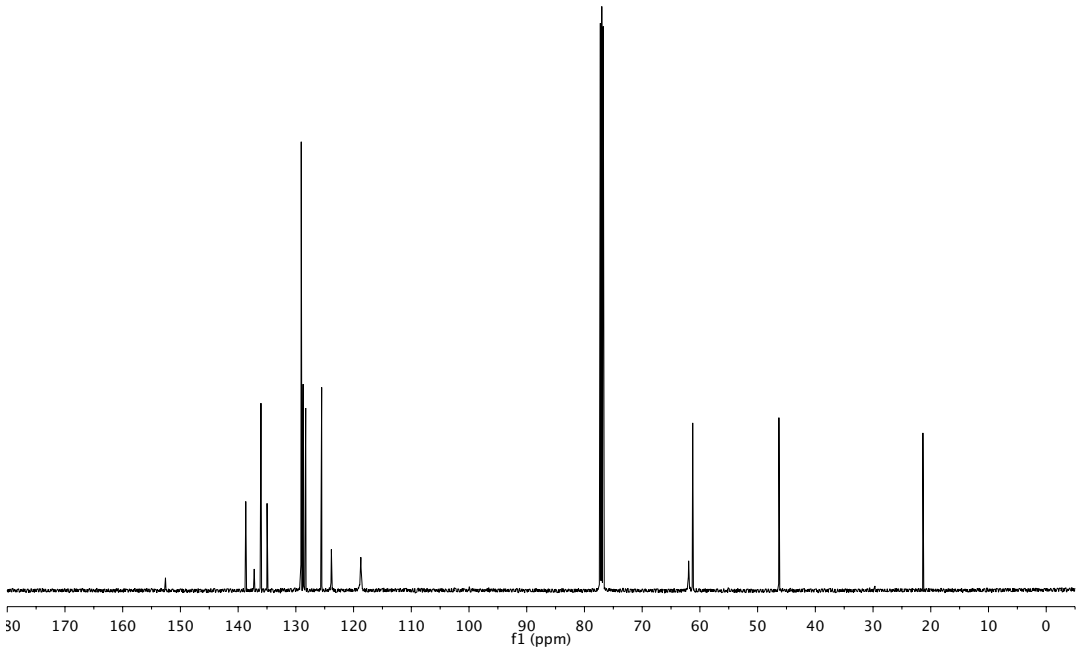
(*R*)-(2-(4-Bromobenzyl)-1,1-dioxido-2,3-dihydroisothiazol-3-yl)methyl phenylcarbamate (3.39)



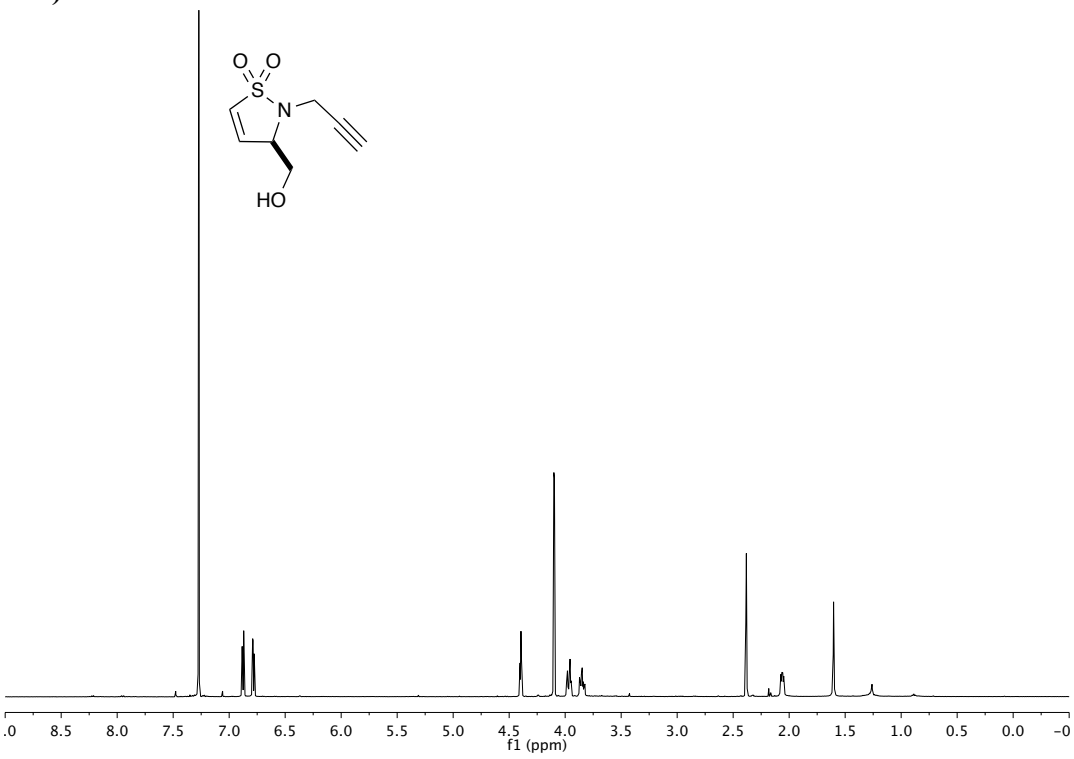


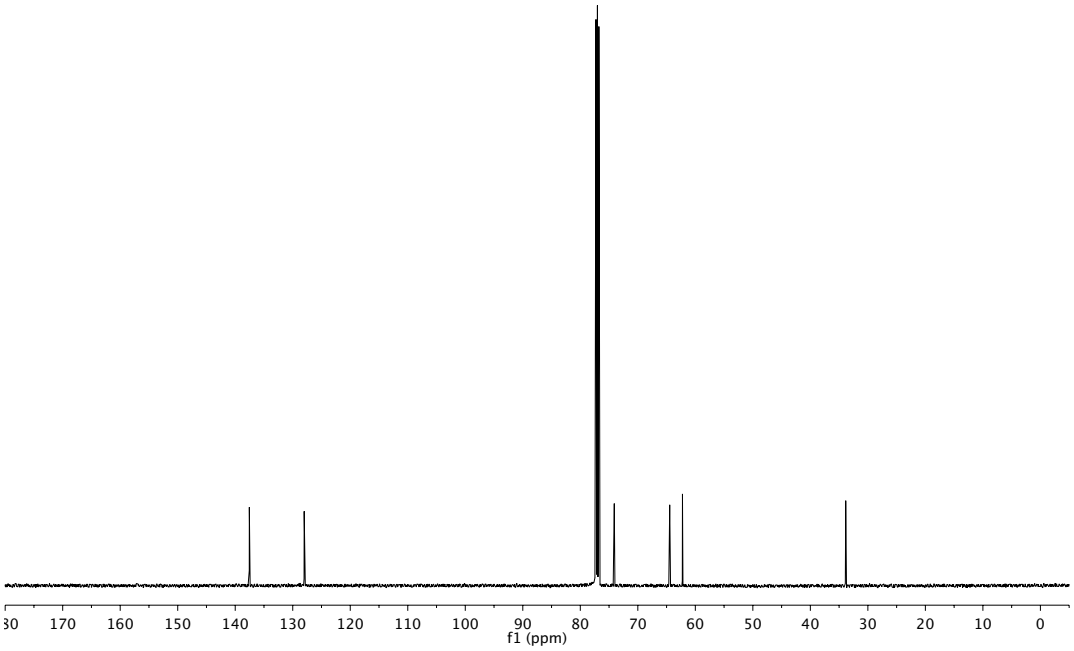
(*R*)-(2-(3-Methylbenzyl)-1,1-dioxido-2,3-dihydroisothiazol-3-yl)methyl phenylcarbamate (3.40)



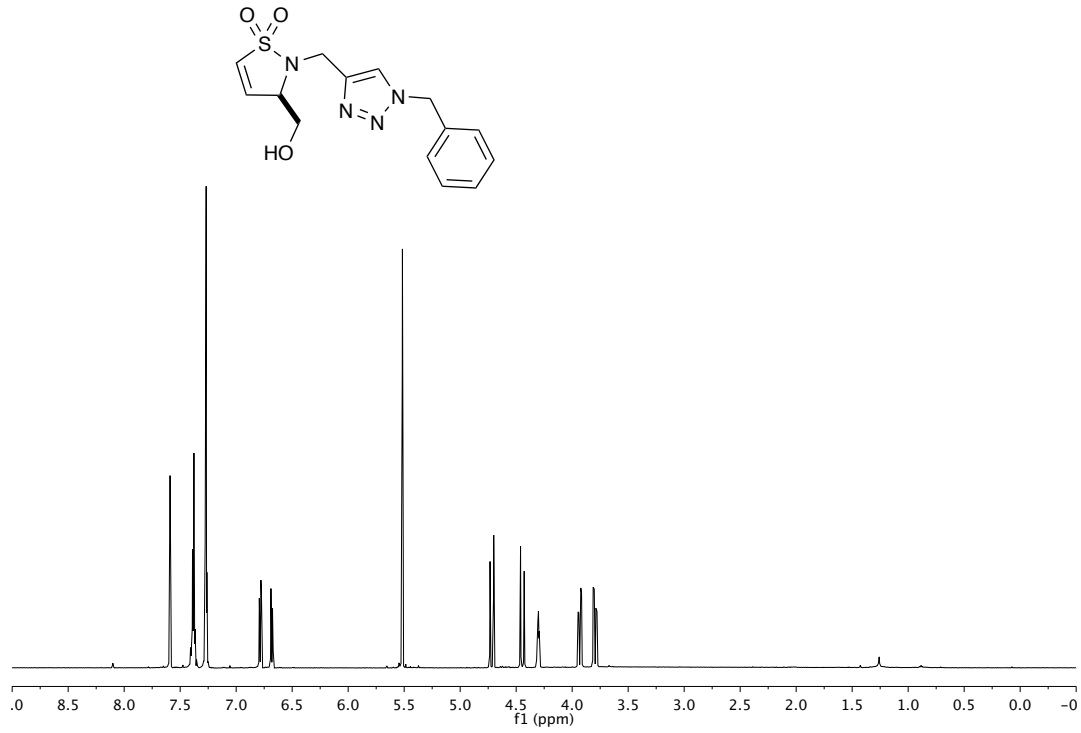


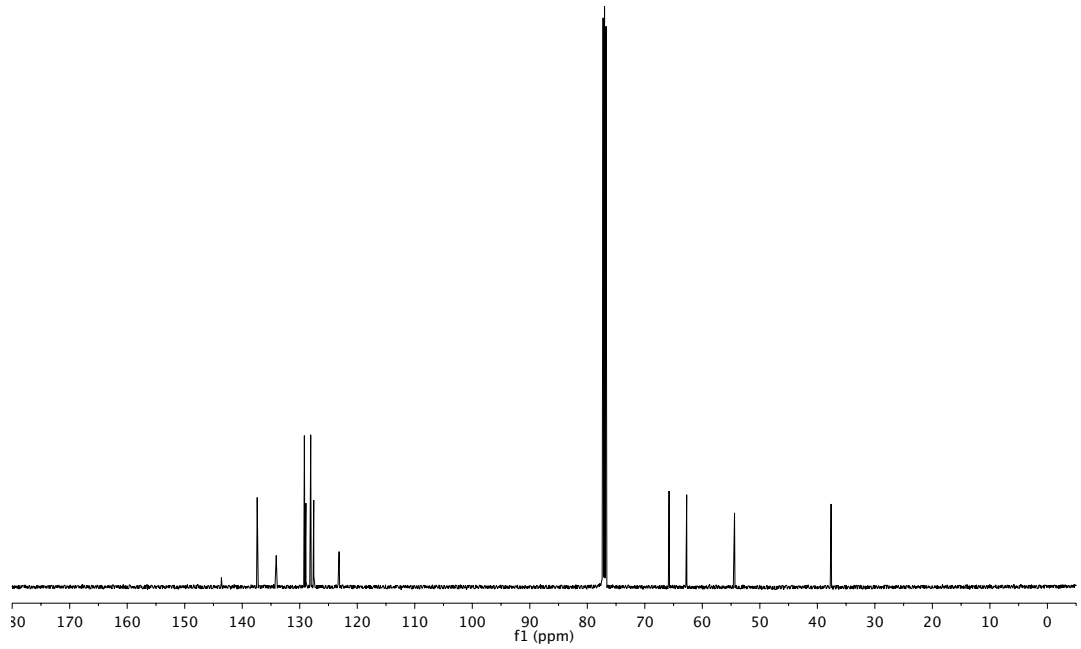
(*R*)-3-(Hydroxymethyl)-2-(prop-2-yn-1-yl)-2,3-dihydroisothiazole 1,1-dioxide (3.41)



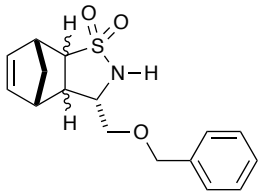


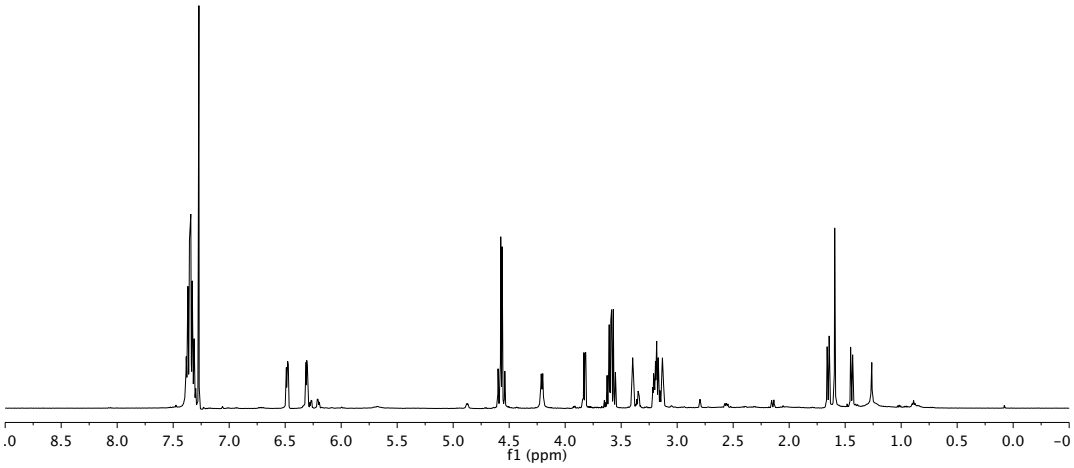
(*R*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(hydroxymethyl)-2,3-dihydroisothiazole 1,1-dioxide (3.42)

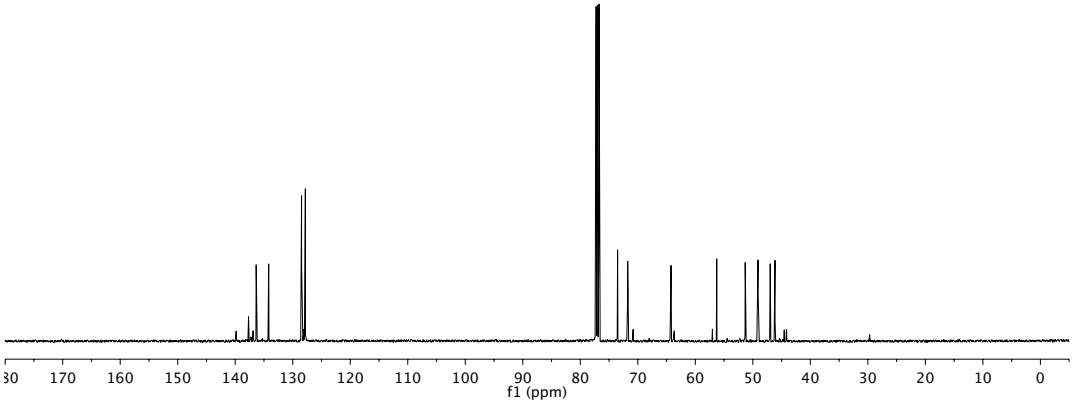




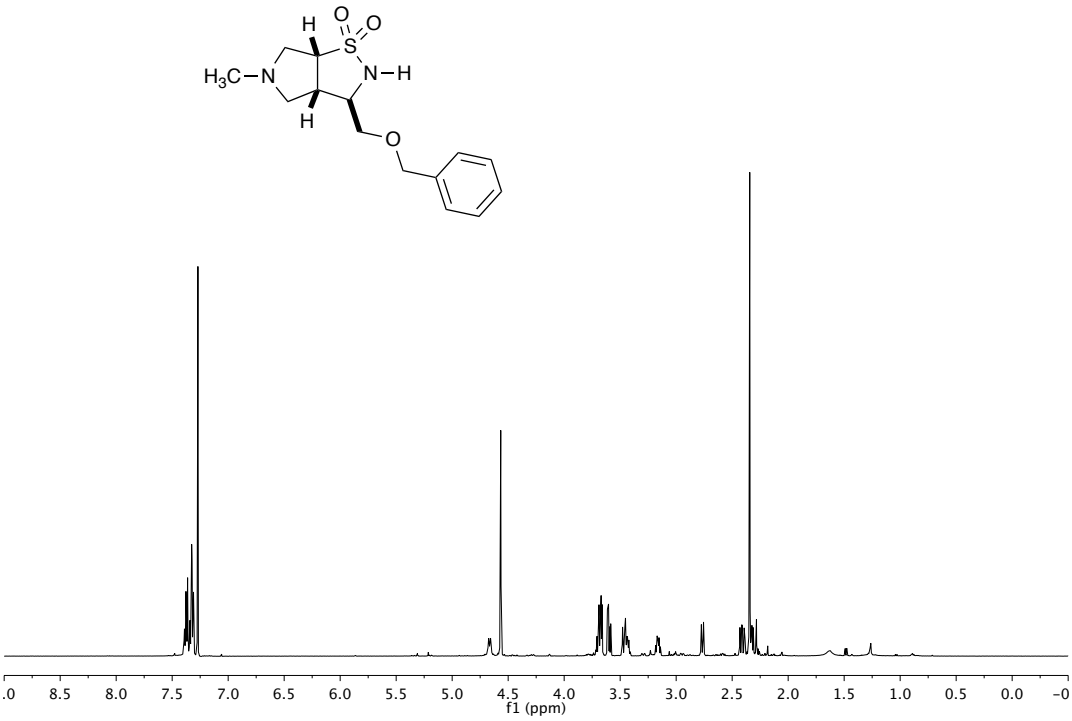
(3*S*,3a*S*,4*S*,7*R*,7a*S*)-3-((Benzyloxy)methyl)-2,3,3a,4,7,7a-hexahydro-4,7-methanobenzo[*d*]isothiazole 1,1-dioxide (3.43)

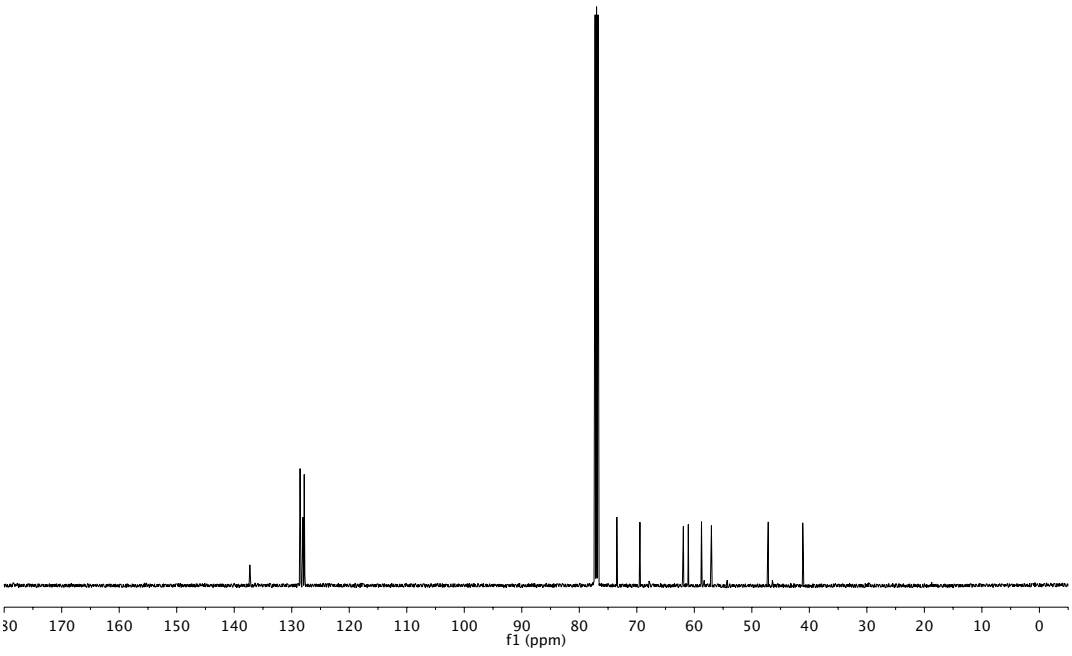




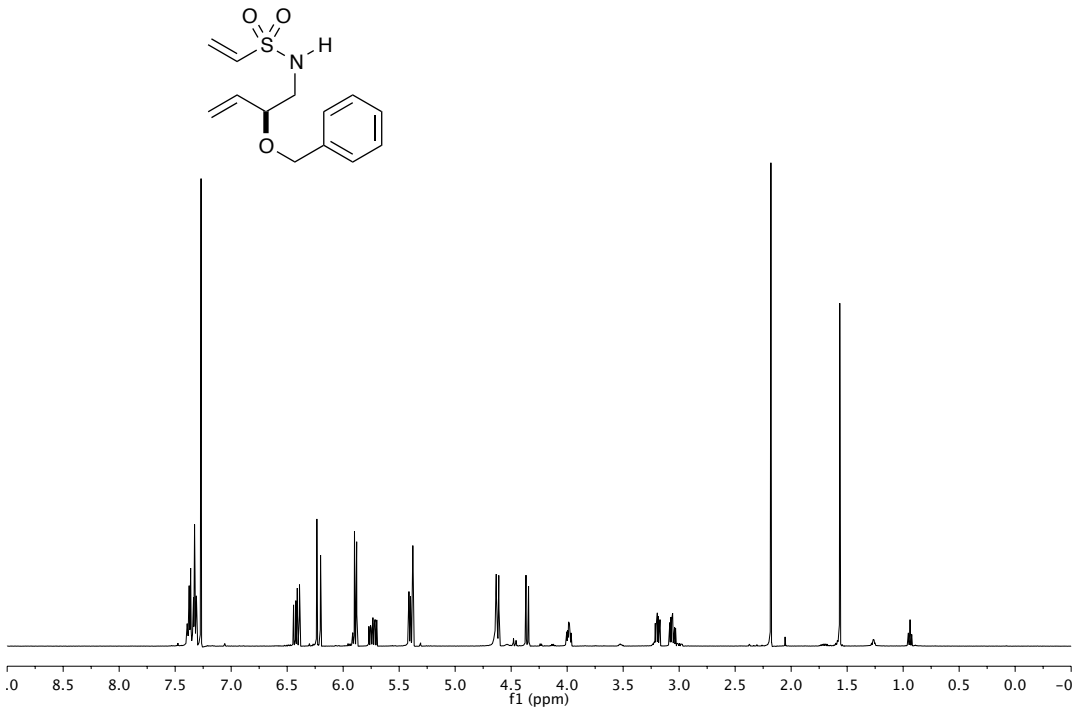


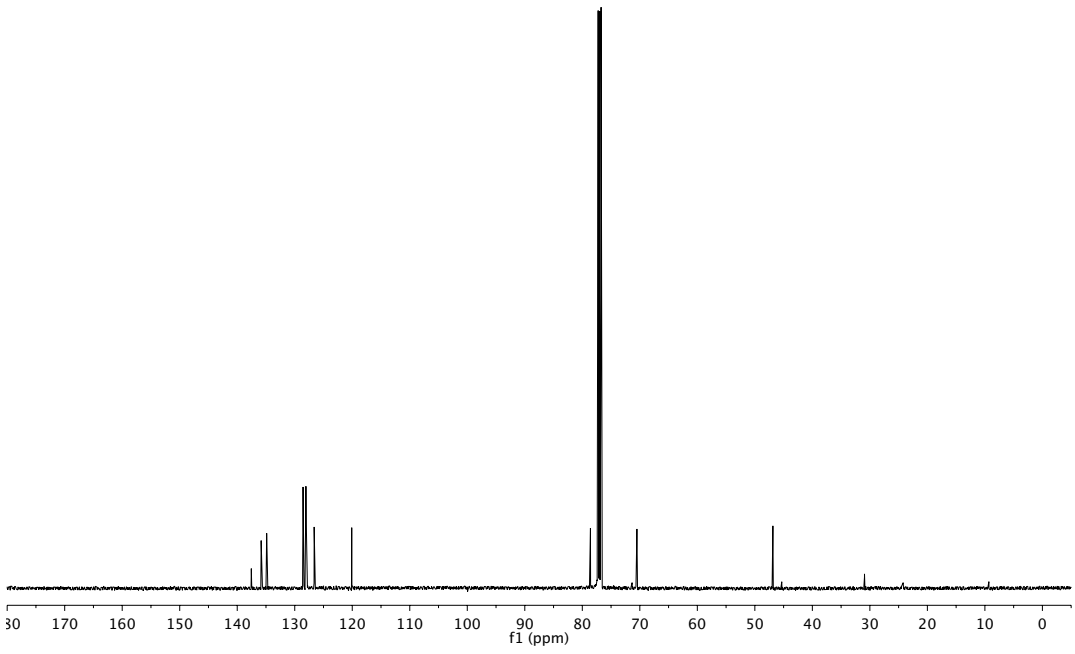
(3*R*,3a*S*,6a*R*)-3-((Benzyloxy)methyl)-5-methylhexahydro-2*H*-pyrrolo[3,4-*d*]isothiazole 1,1-dioxide (3.44)



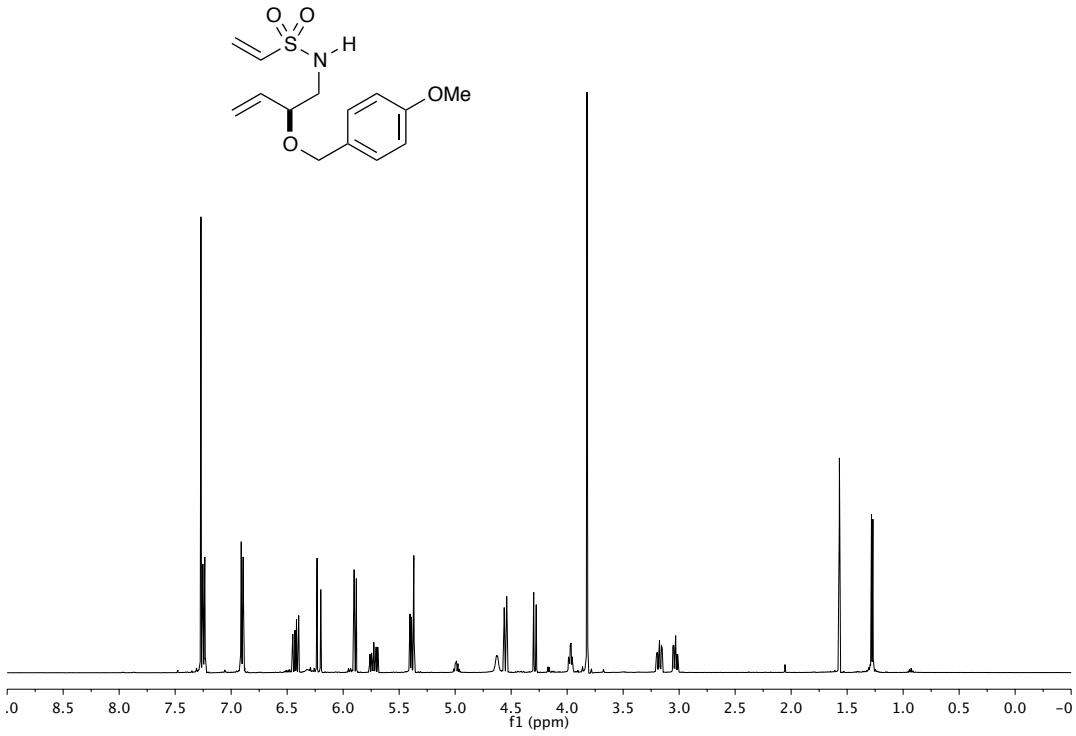


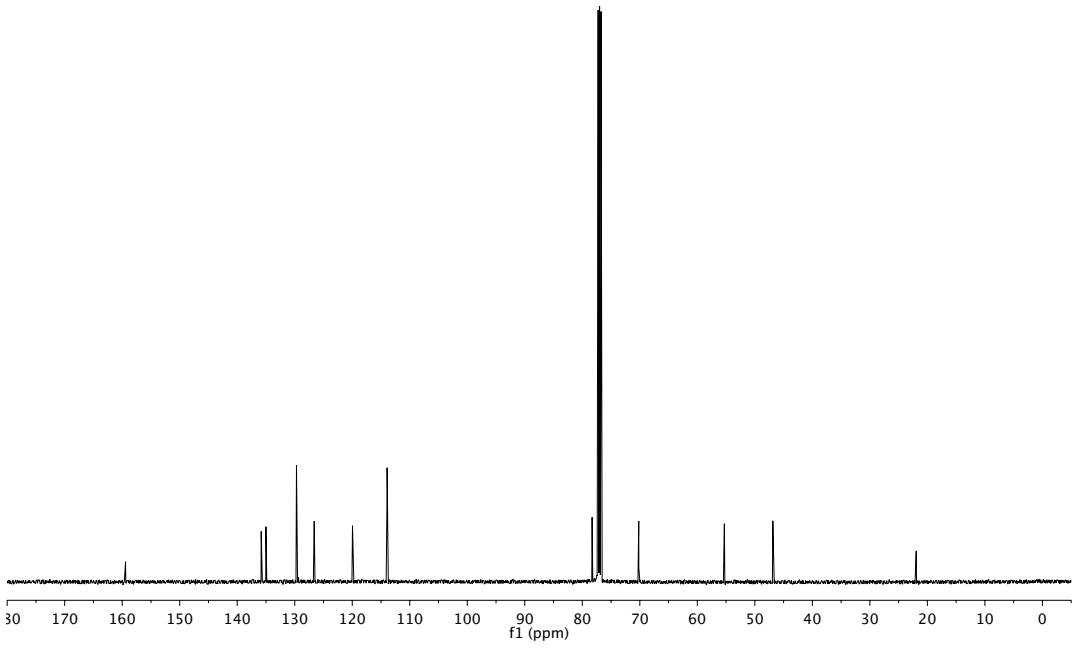
(*S*)-*N*-(2-(Benzyloxy)but-3-en-1-yl)ethenesulfonamide (3.49)



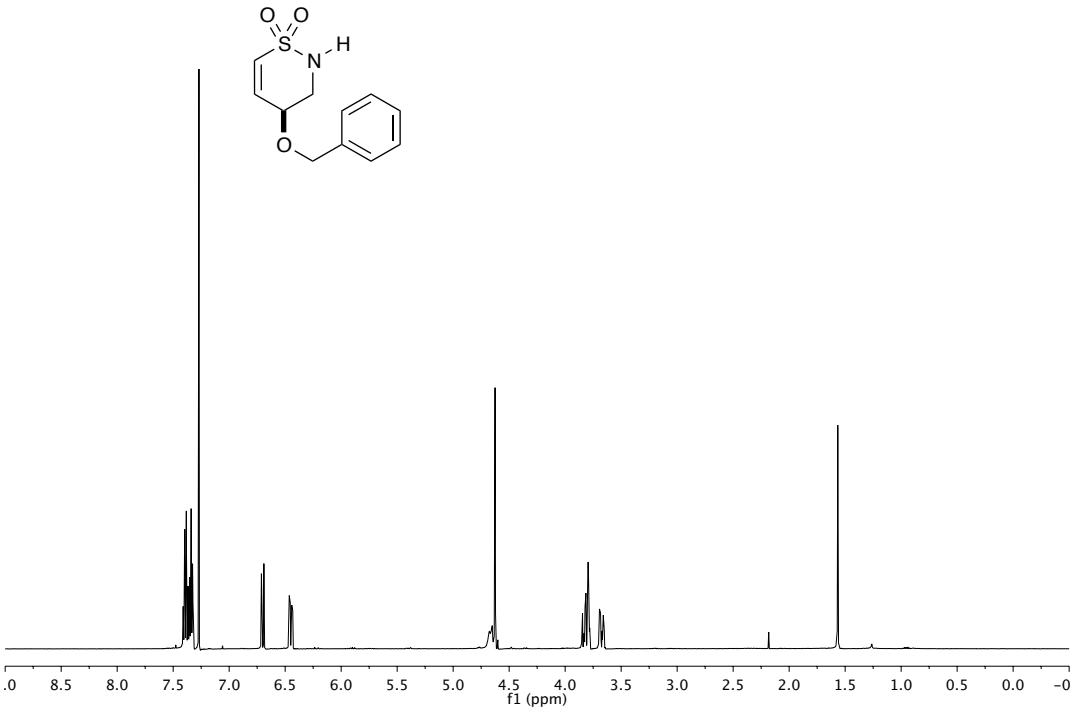


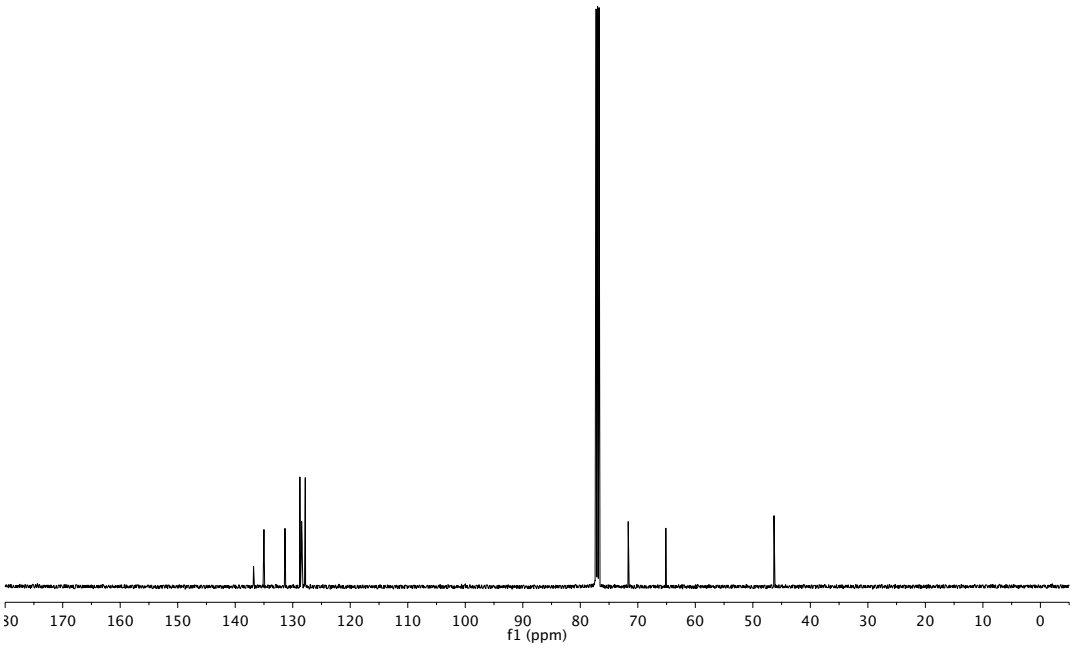
(*S*)-*N*-(2-((4-Methoxybenzyl)oxy)but-3-en-1-yl)ethenesulfonamide (3.50)



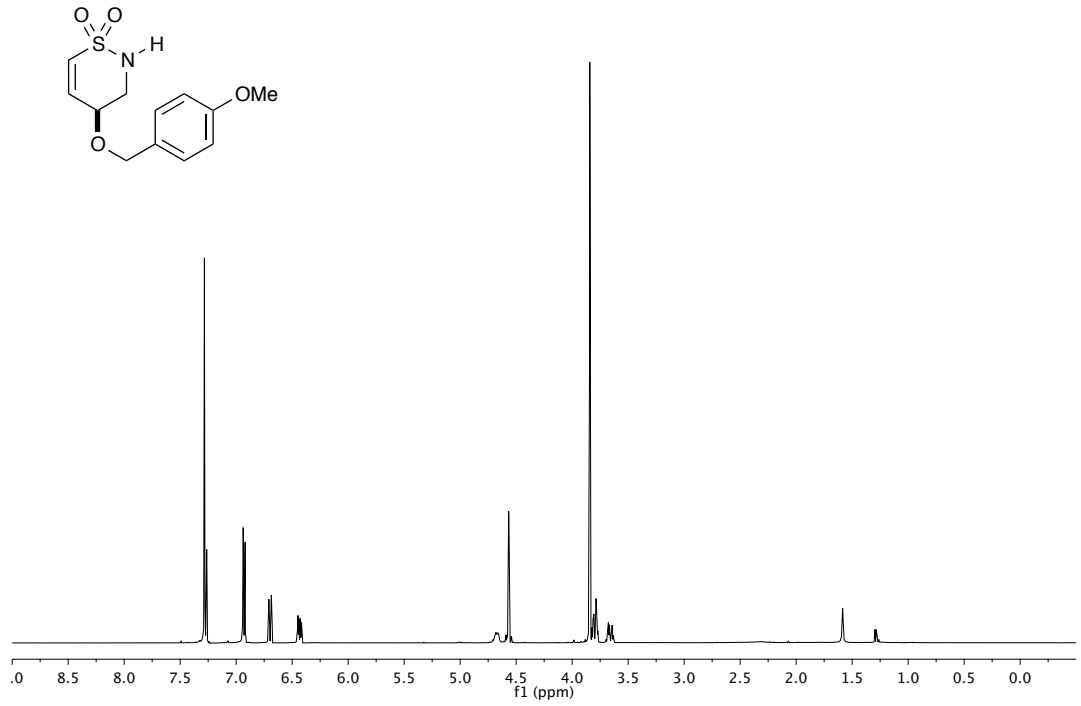


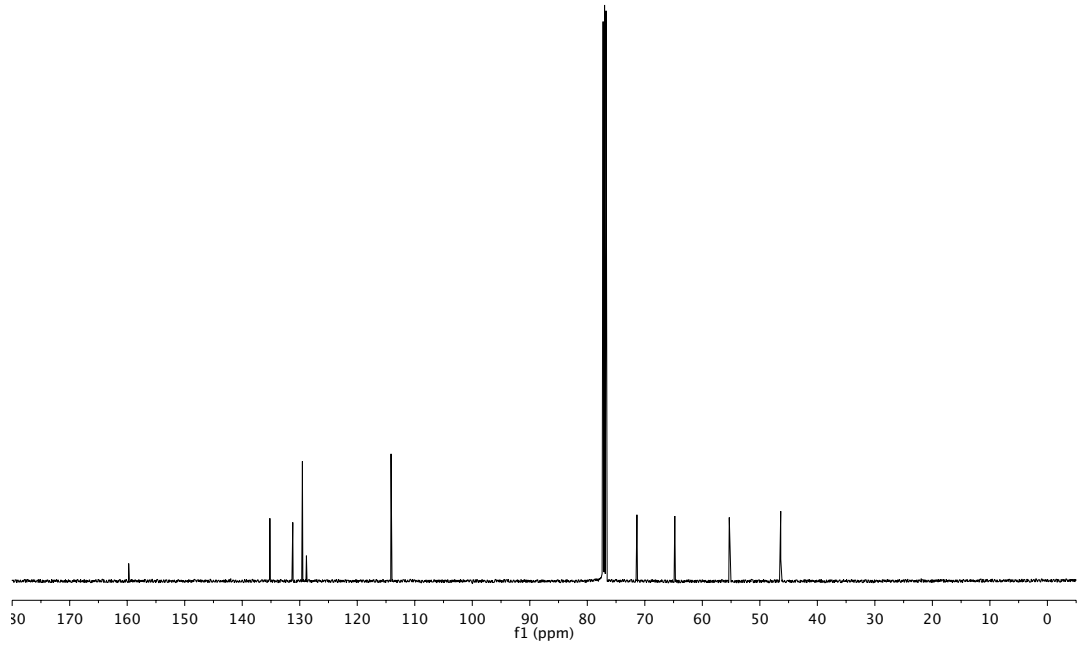
(*S*)-4-(Benzyloxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.51)



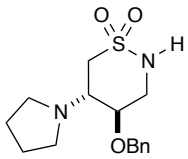


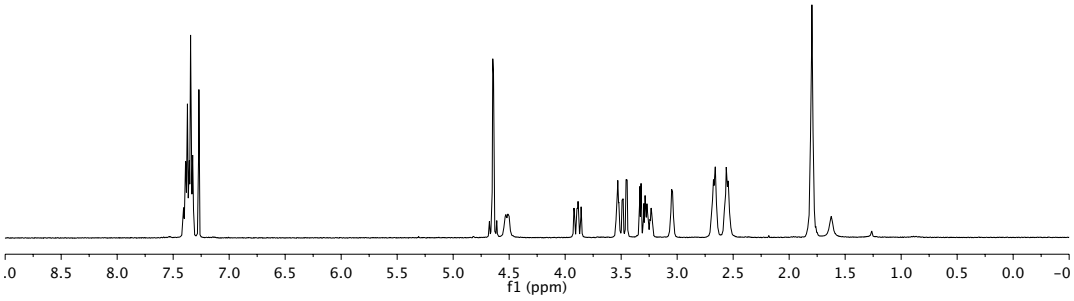
(*S*)-4-((4-Methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.52)

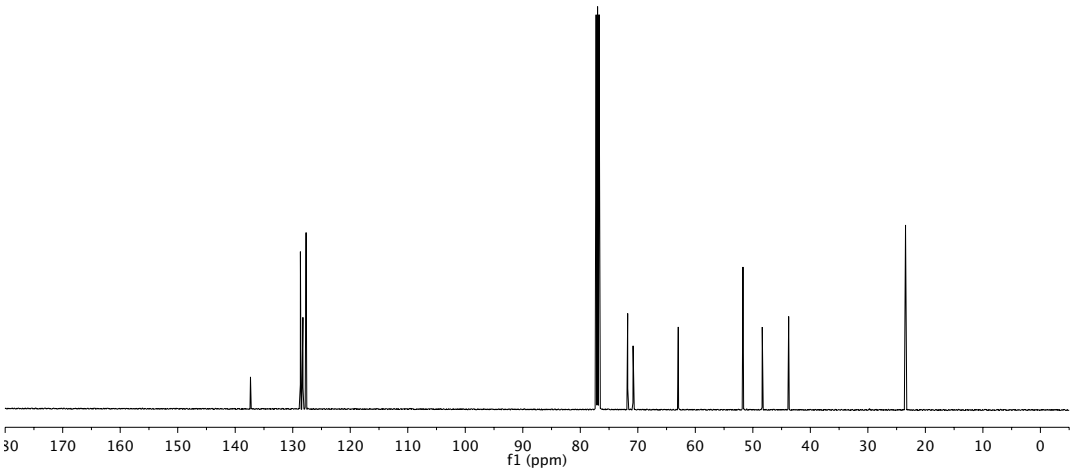




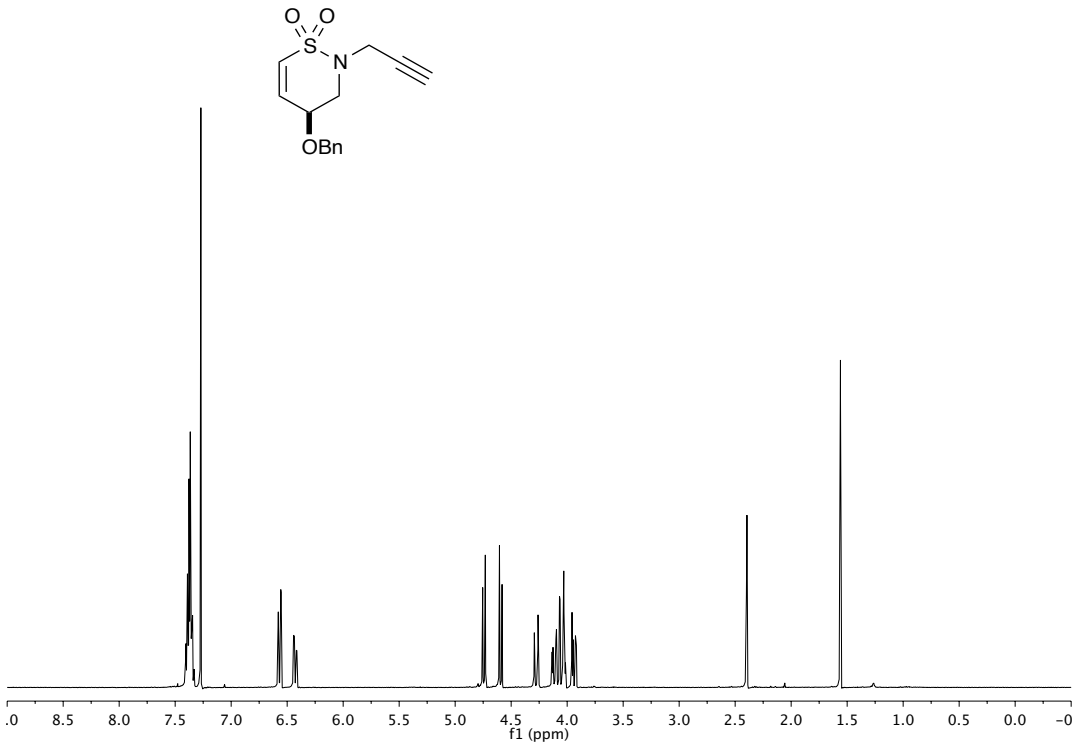
(4*R*,5*S*)-4-(Benzyloxy)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.53)

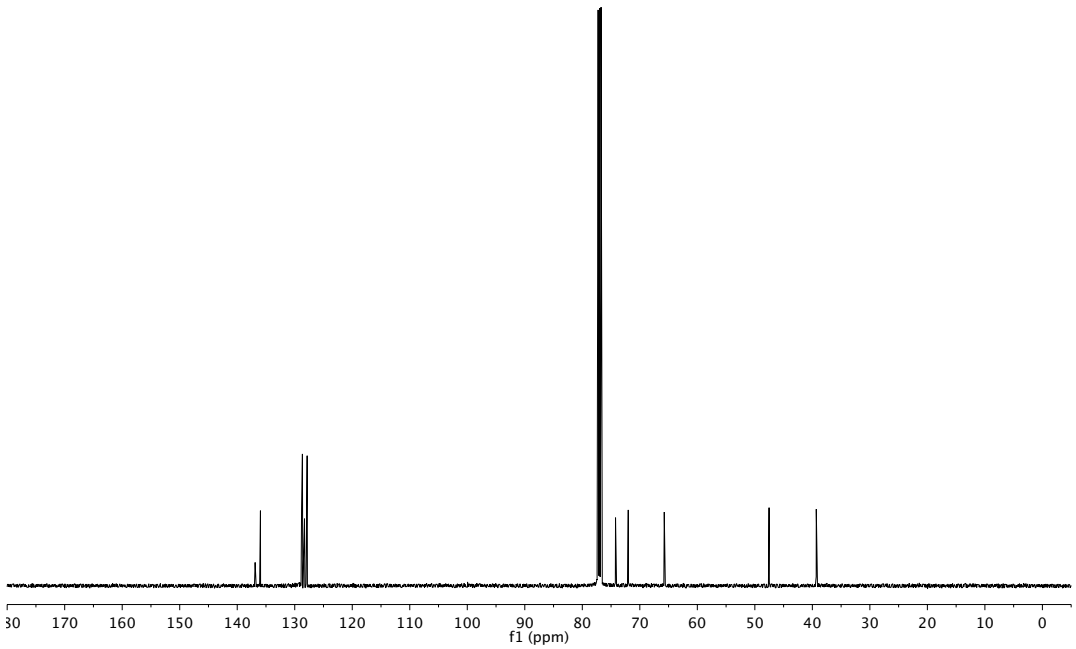




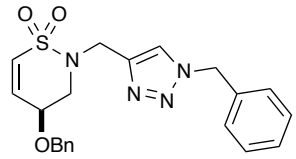


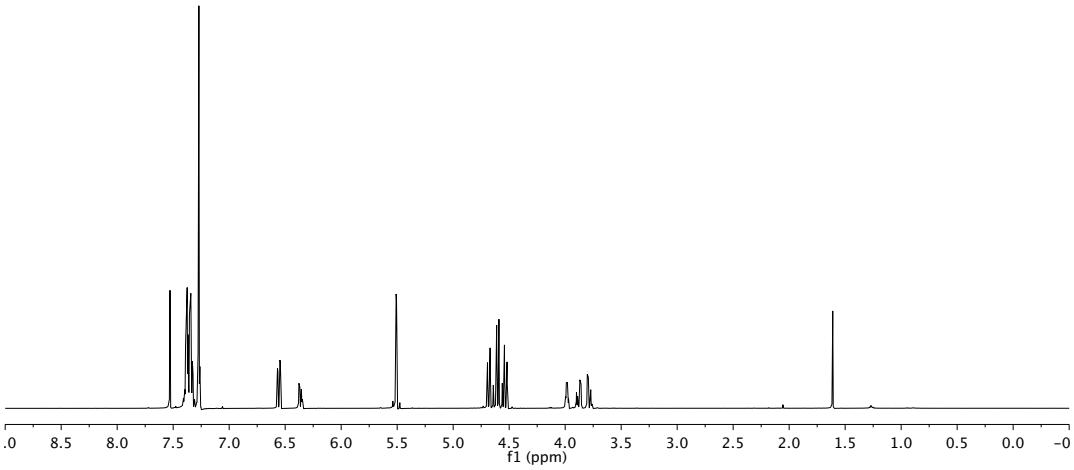
(*S*)-4-(Benzyloxy)-2-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.54)

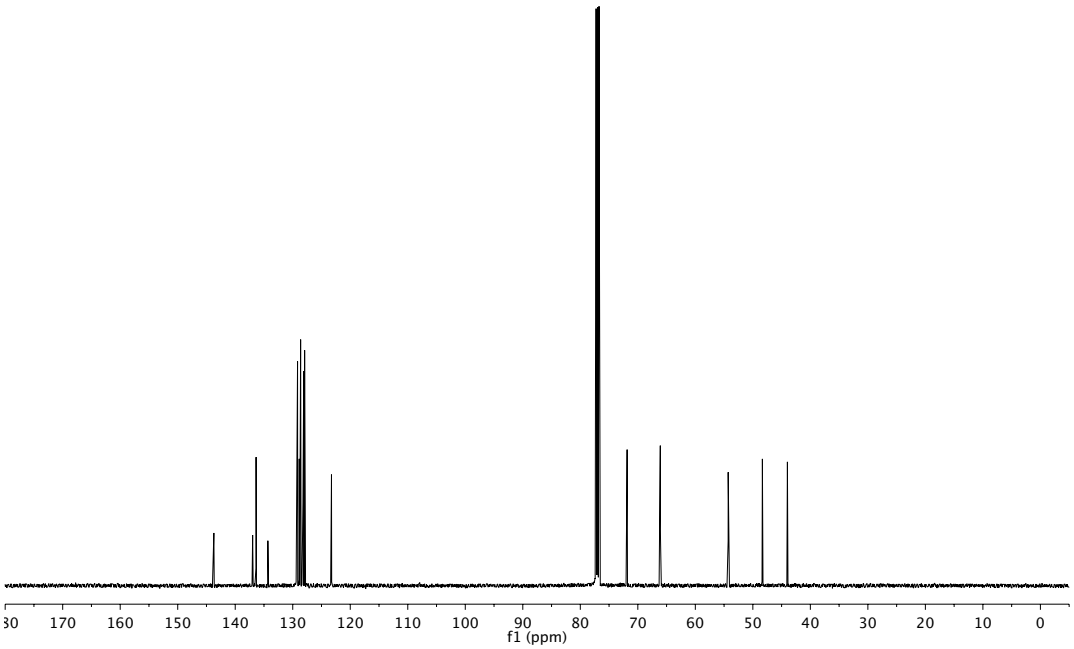




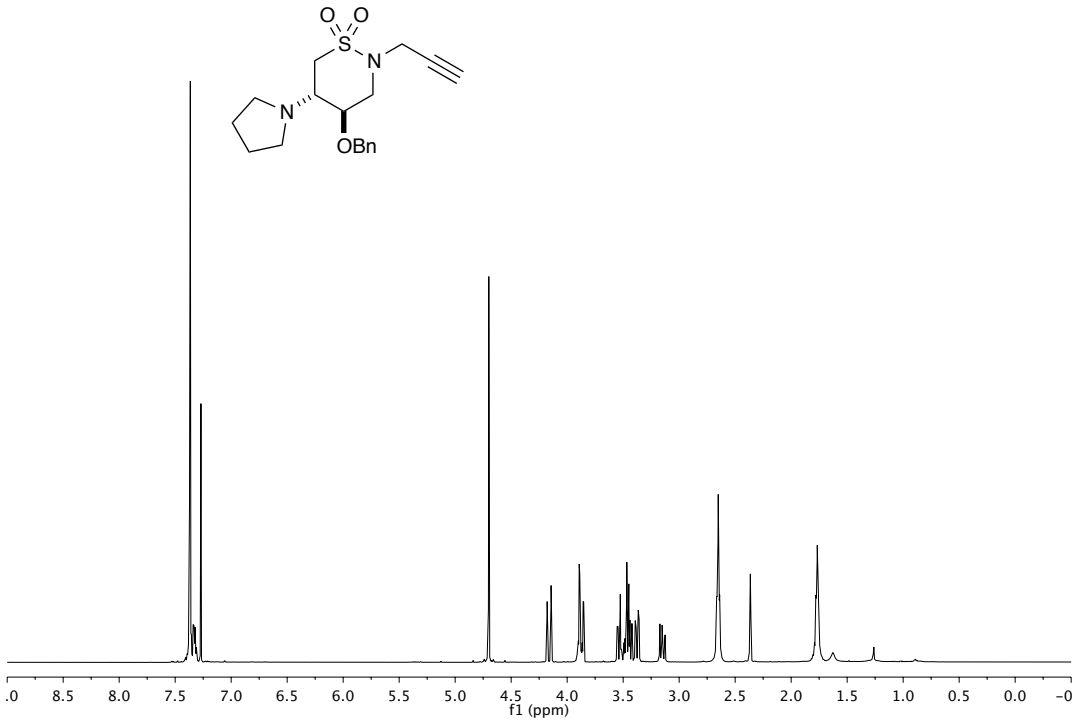
(*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-(benzyloxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.55)

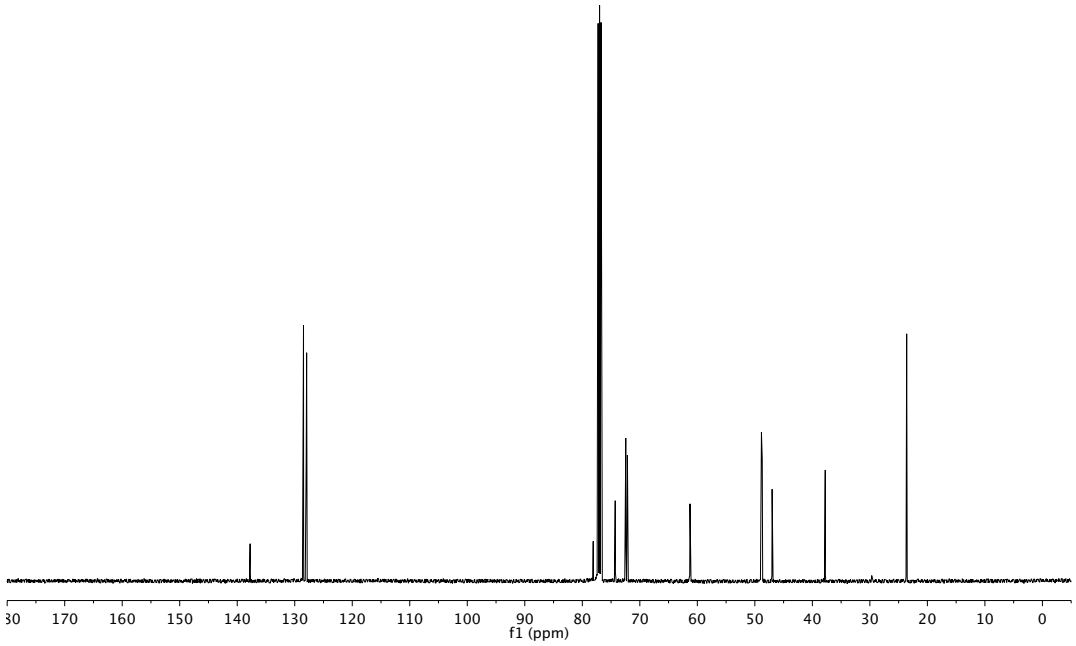




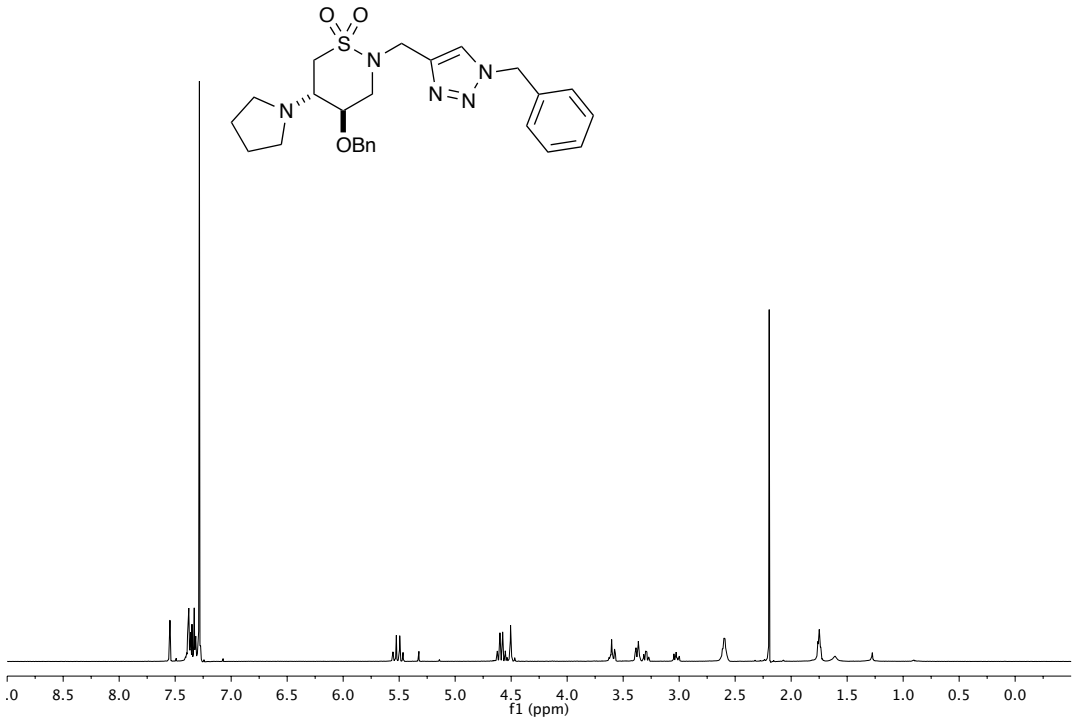


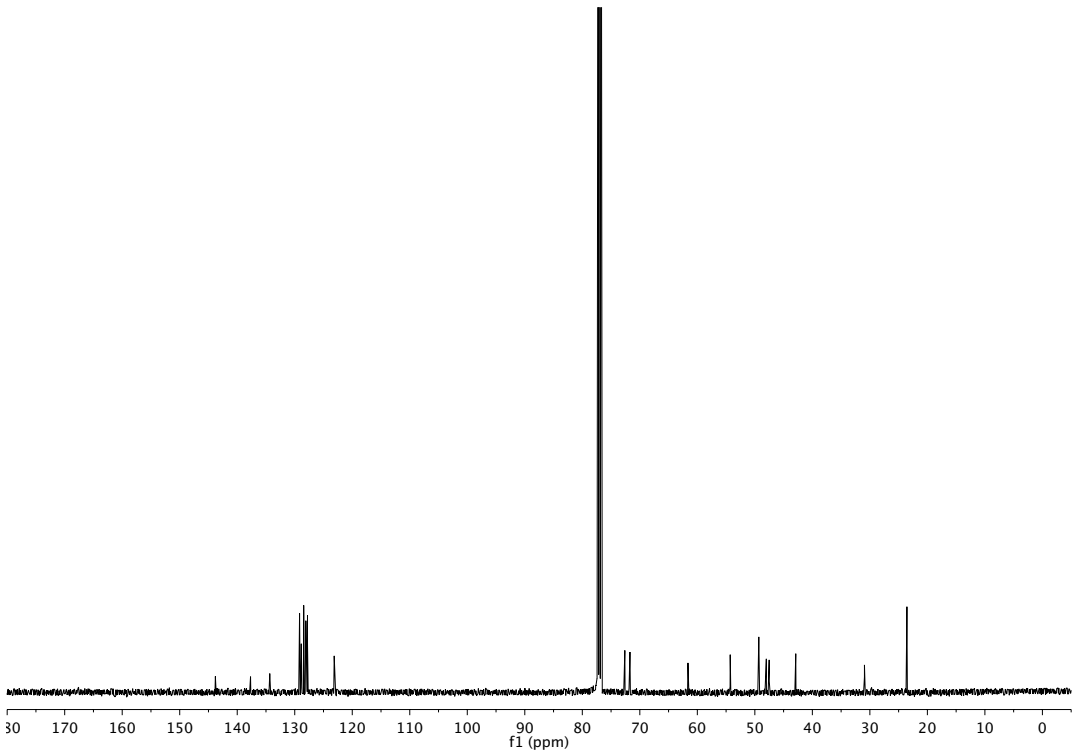
(4*R*,5*S*)-4-(Benzyloxy)-2-(prop-2-yn-1-yl)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.56)



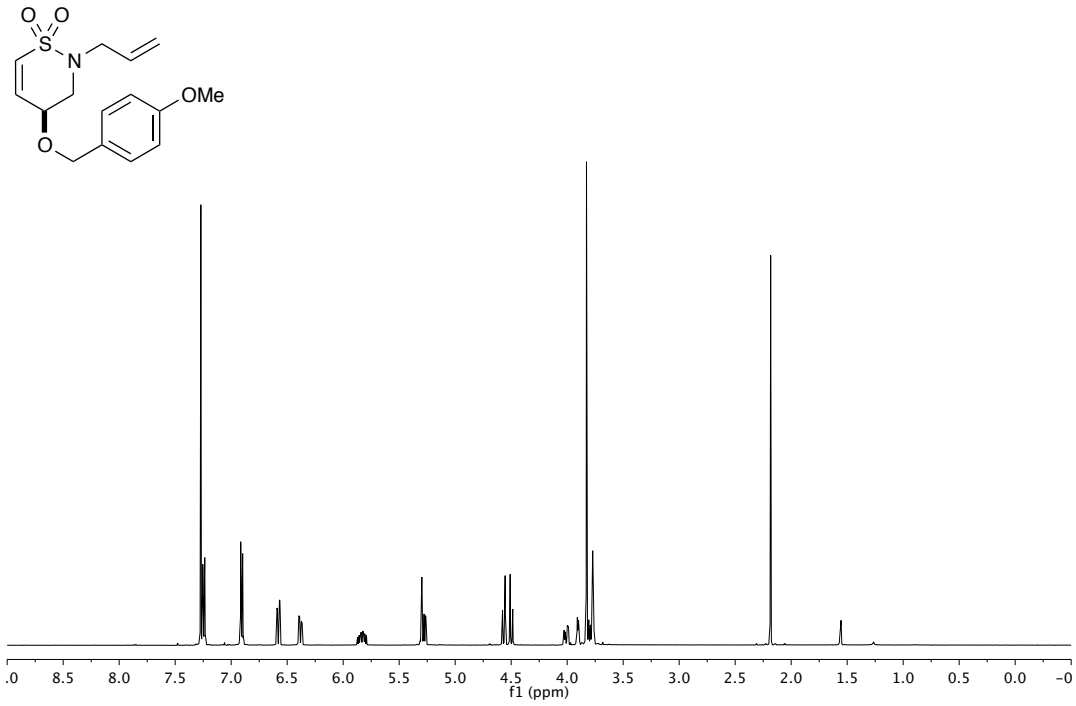


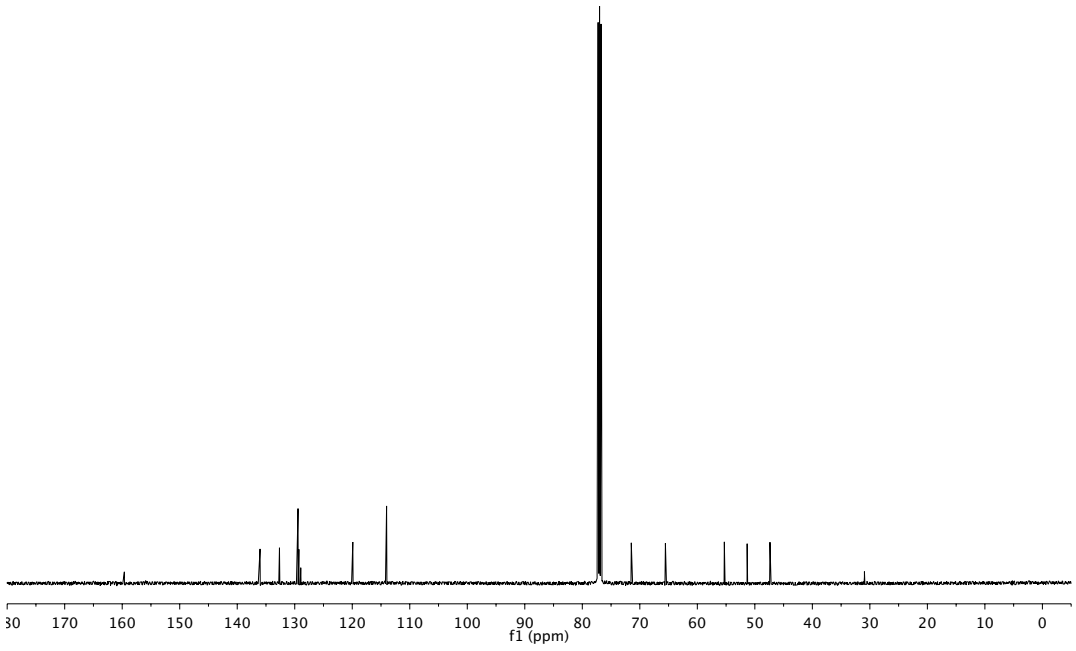
(4*R*,5*S*)-2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-(benzyloxy)-5-(pyrrolidin-1-yl)-1,2-thiazinane 1,1-dioxide (3.57)



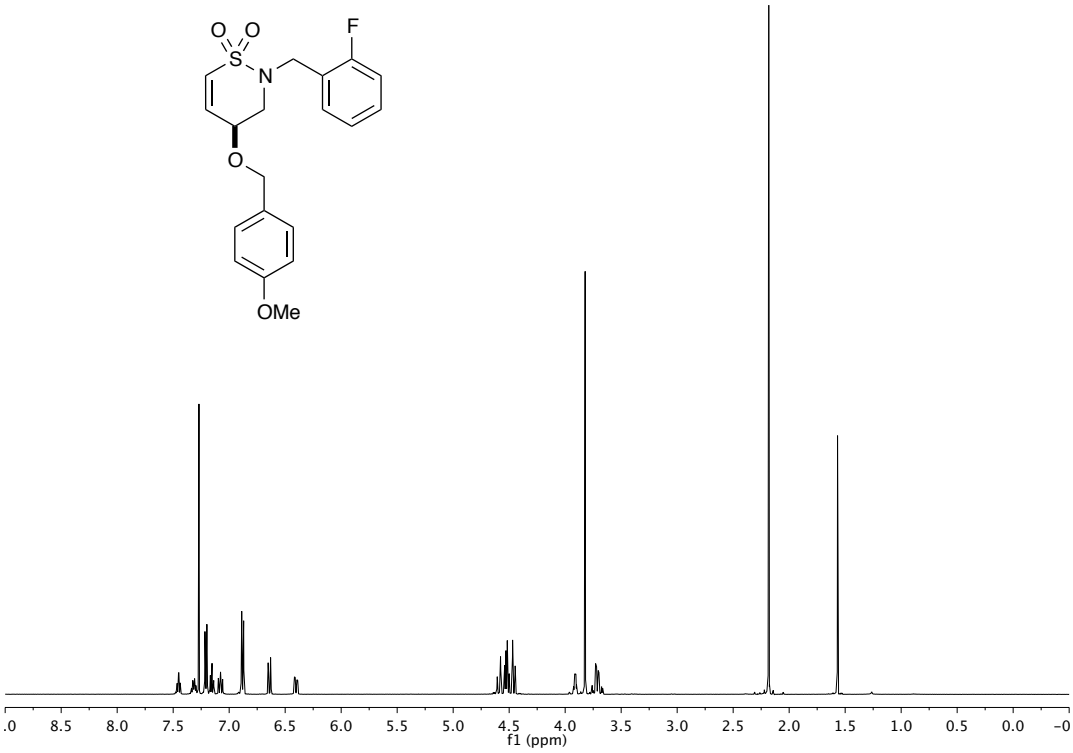


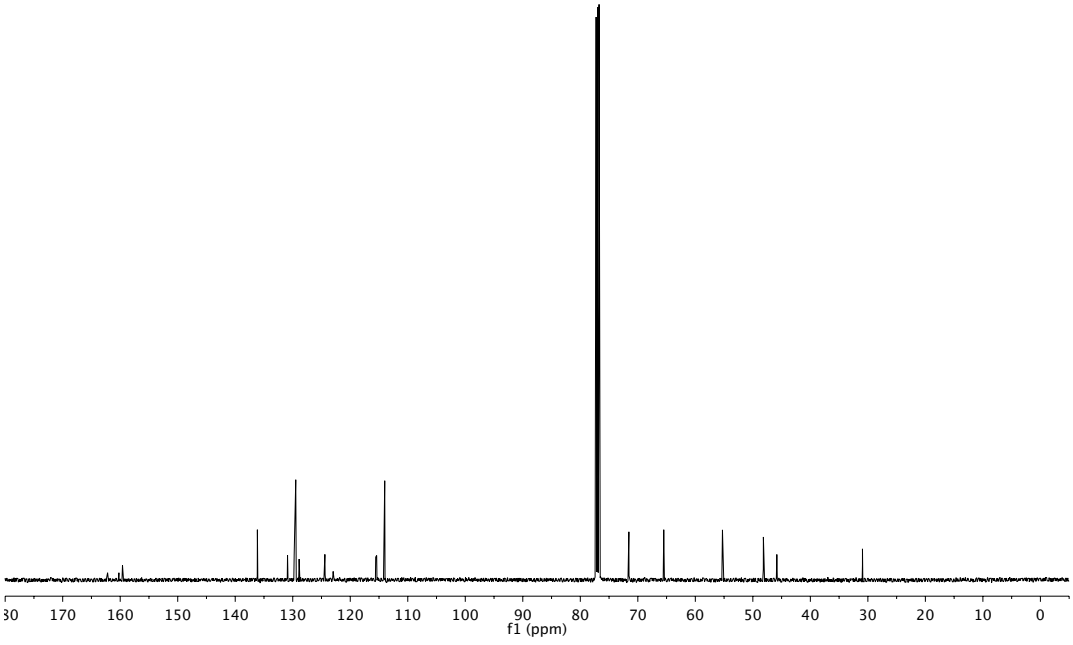
(*S*)-2-Allyl-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.58)



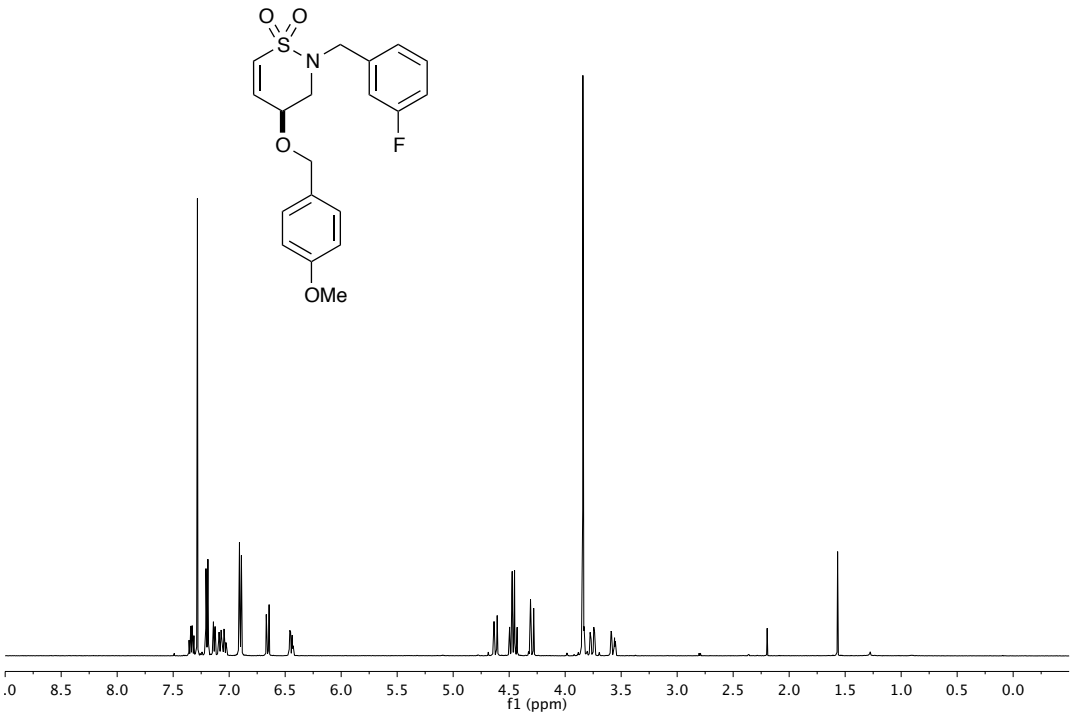


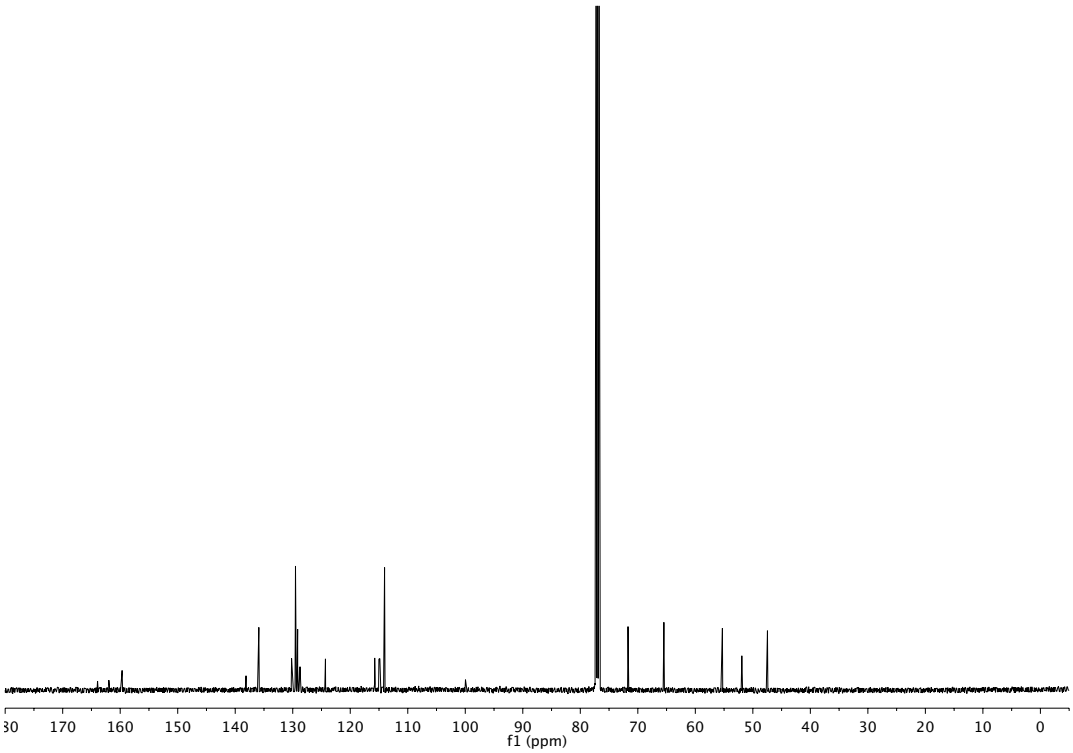
(*S*)-2-(2-Fluorobenzyl)-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.59)



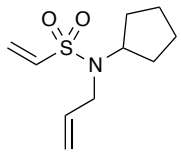


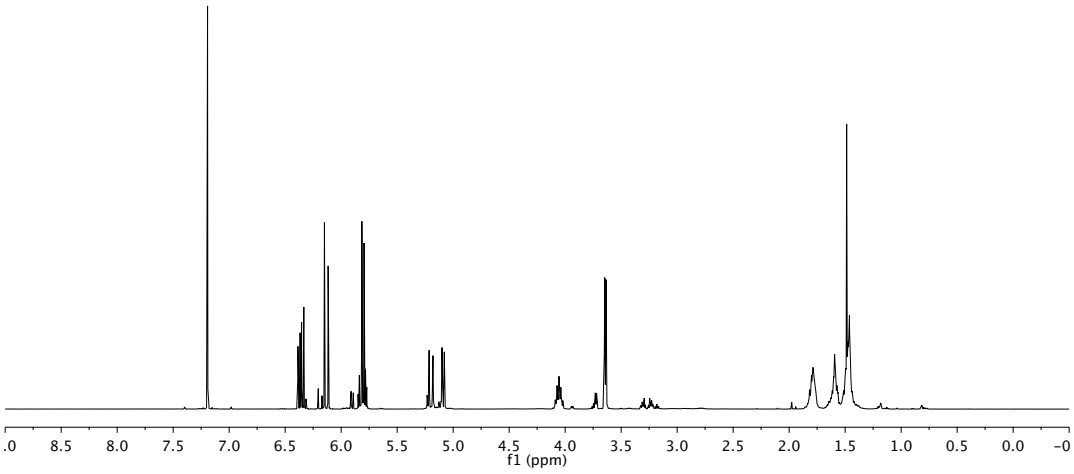
(*S*)-2-(3-Fluorobenzyl)-4-((4-methoxybenzyl)oxy)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (3.60)

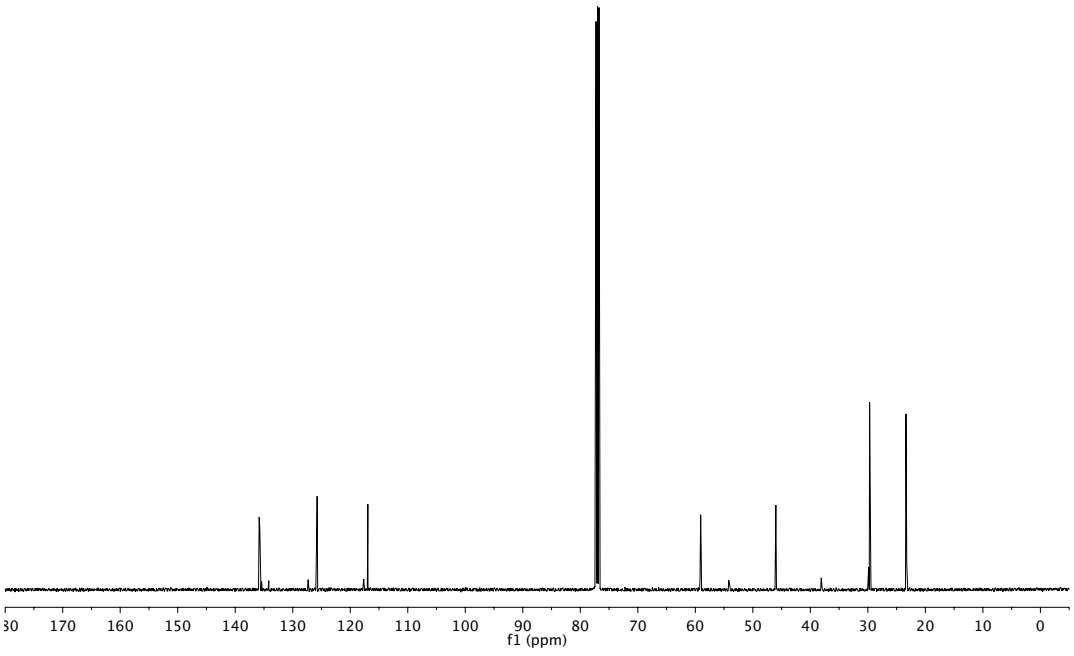




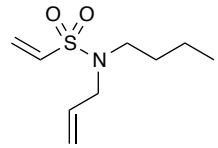
_N_-Allyl-_N_-cyclopentylethenesulfonamide (3.61a)

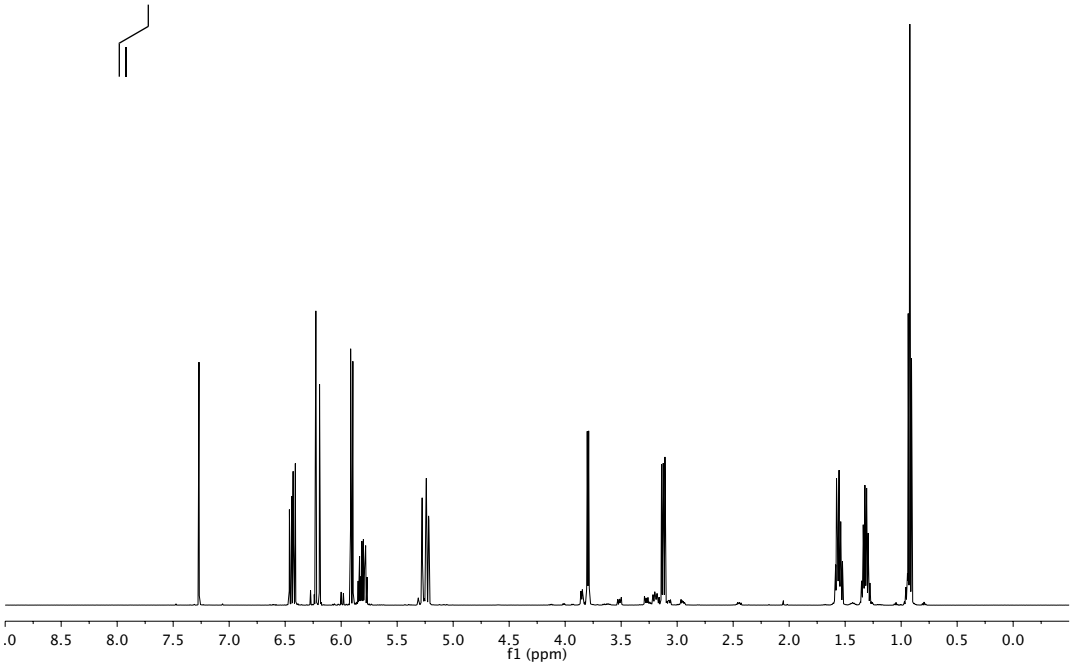


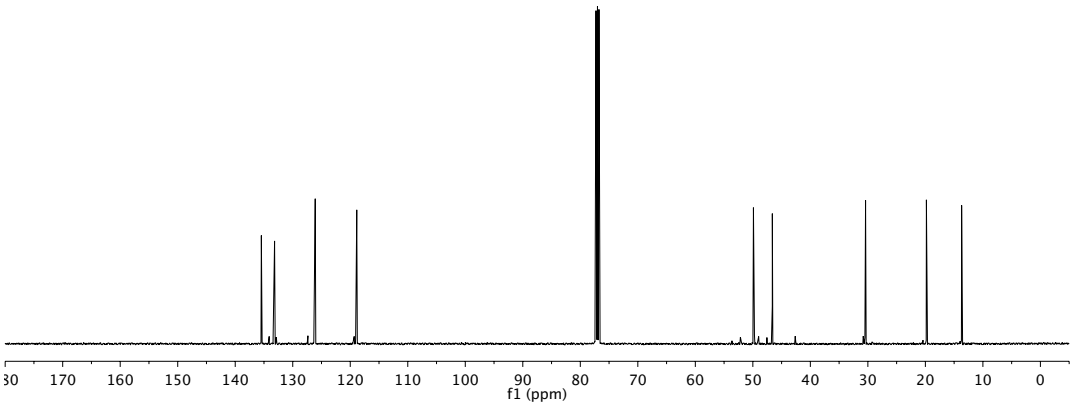




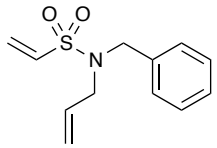
_N_-Allyl-_N_-butylethenesulfonamide (3.61b)

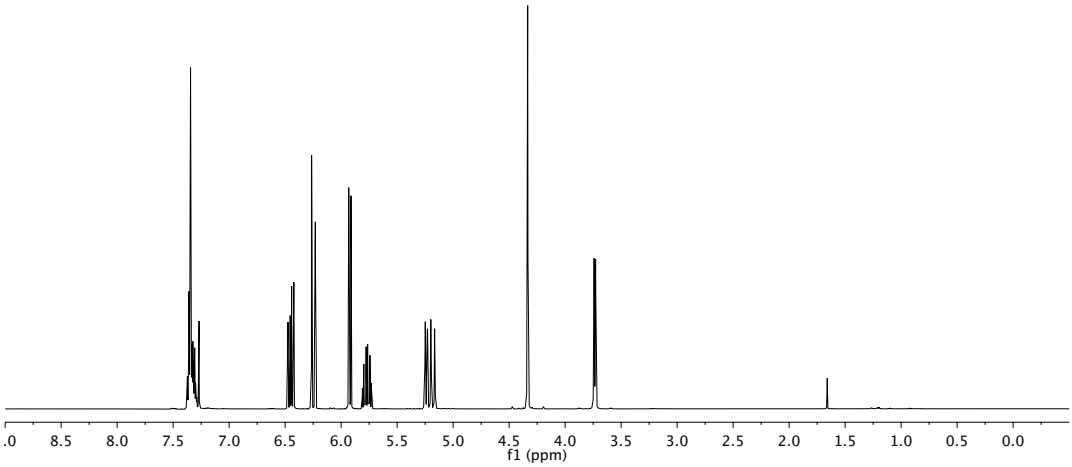


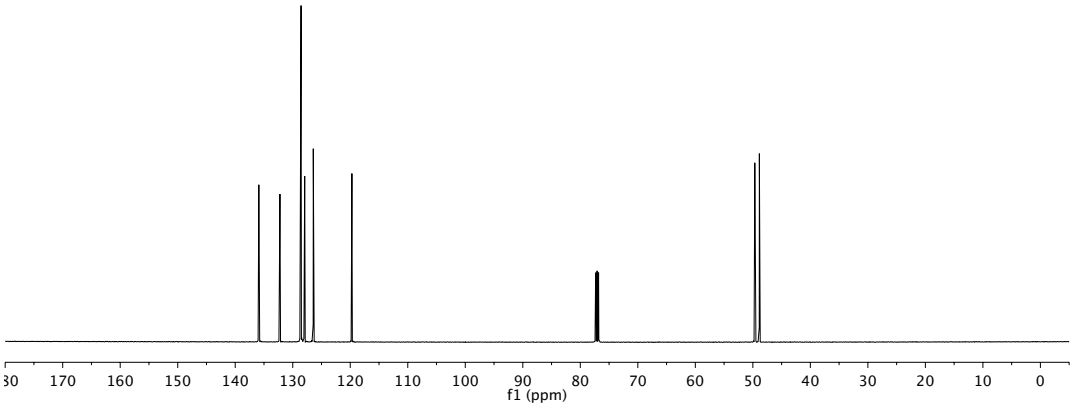




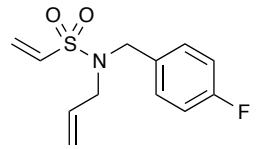
_N_-Allyl-_N_-benzylethenesulfonamide (3.61c)

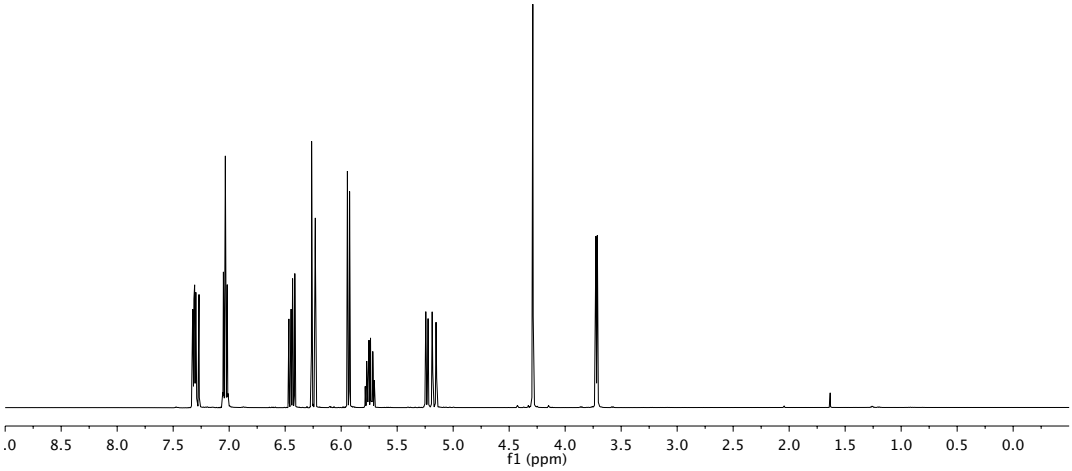


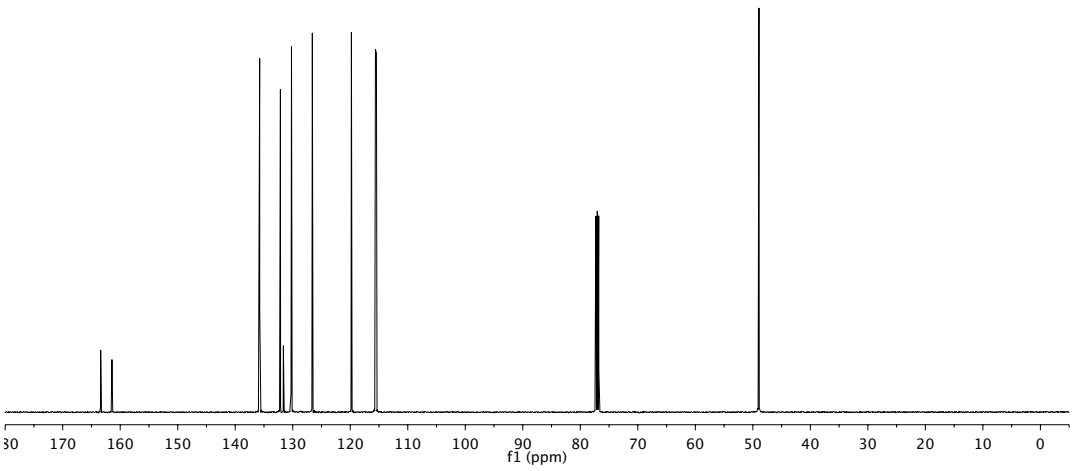




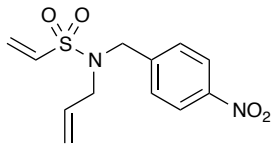
***N*-Allyl-*N*-(4-fluorobenzyl)ethenesulfonamide (3.61d)**

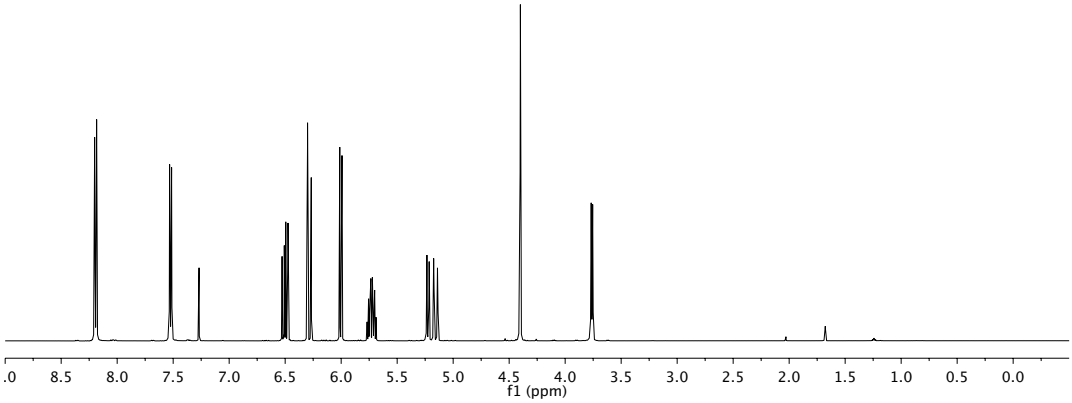


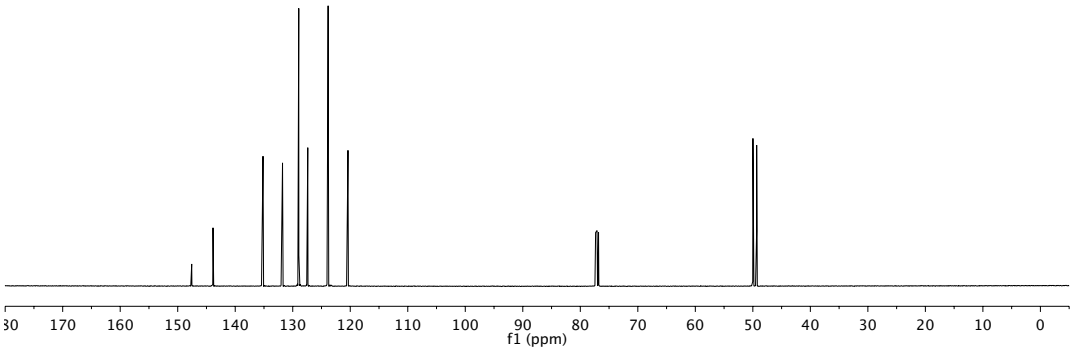




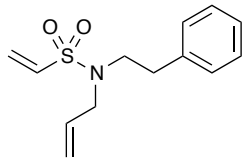
_N_-Allyl-_N_-(4-nitrobenzyl)ethenesulfonamide (3.61e)

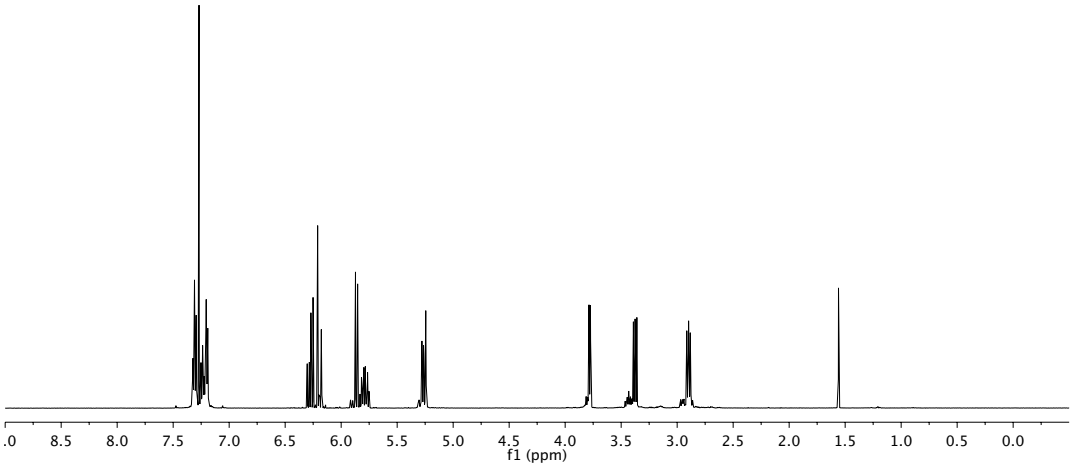


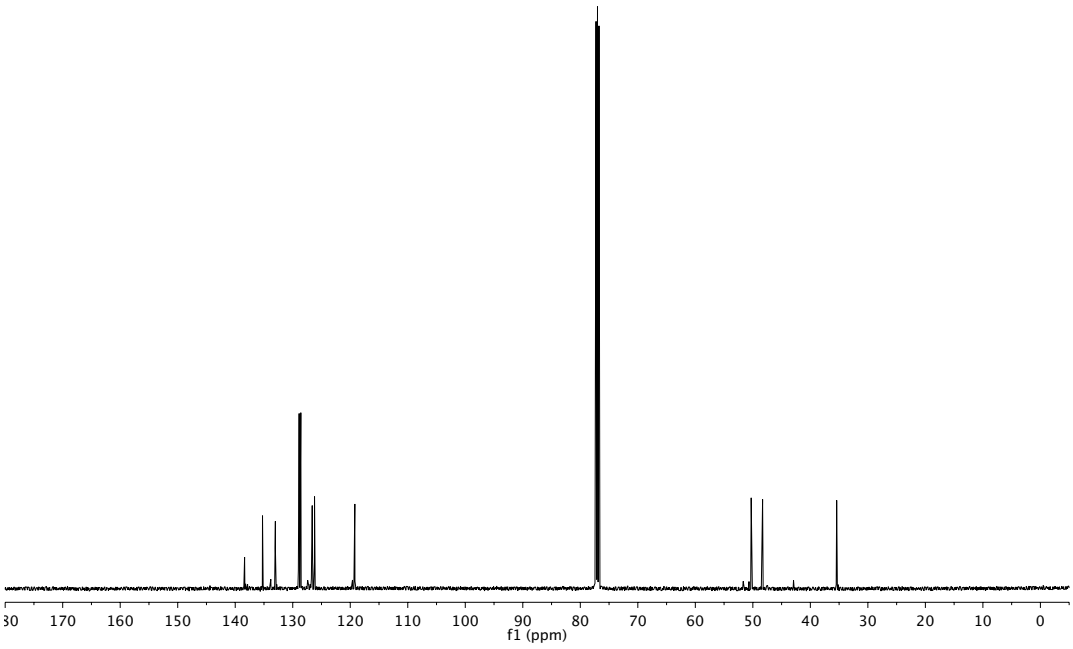




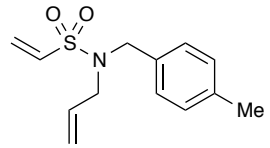
***N*-Allyl-*N*-phenethylethenesulfonamide (3.61f)**

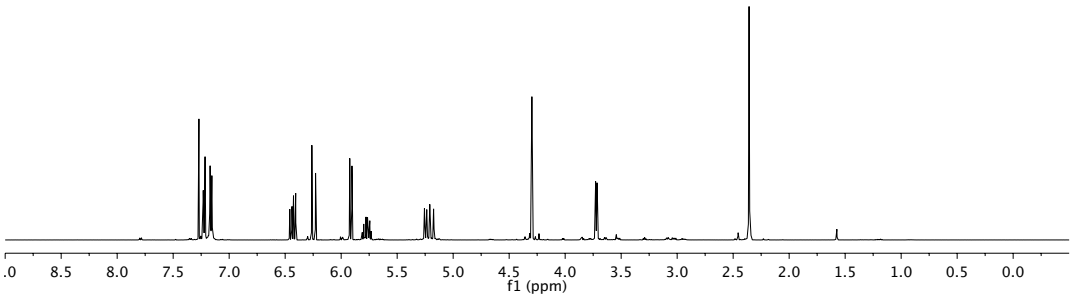


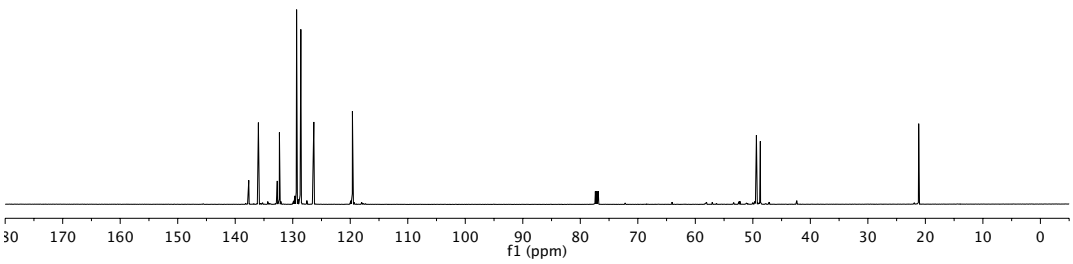




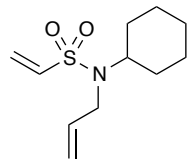
***N*-allyl-*N*-(4-methylbenzyl)ethenesulfonamide (3.61g)**

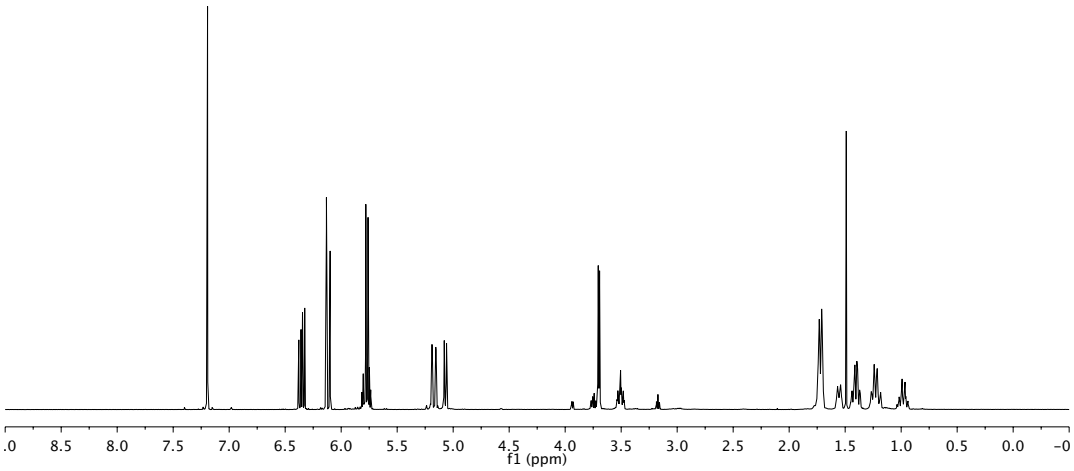


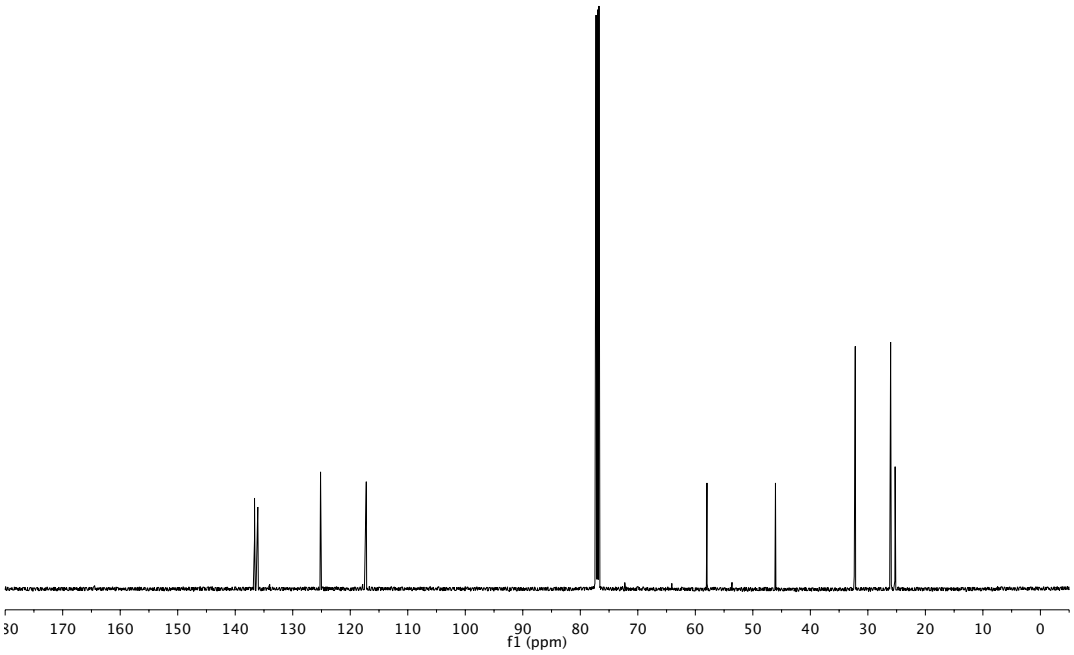




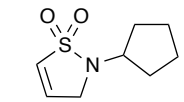
_N_-Allyl-_N_-cyclohexylethenesulfonamide (3.61h)

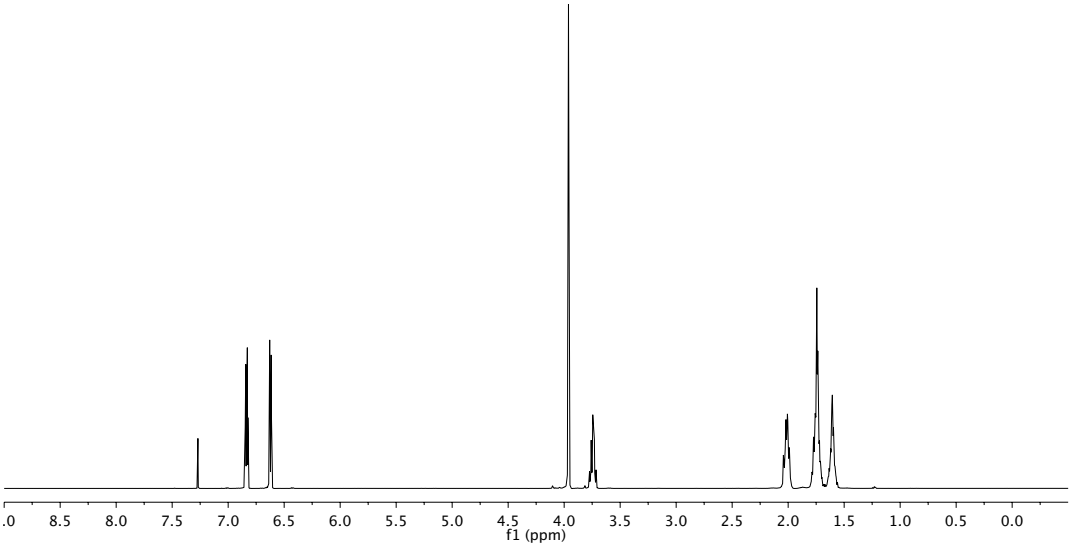


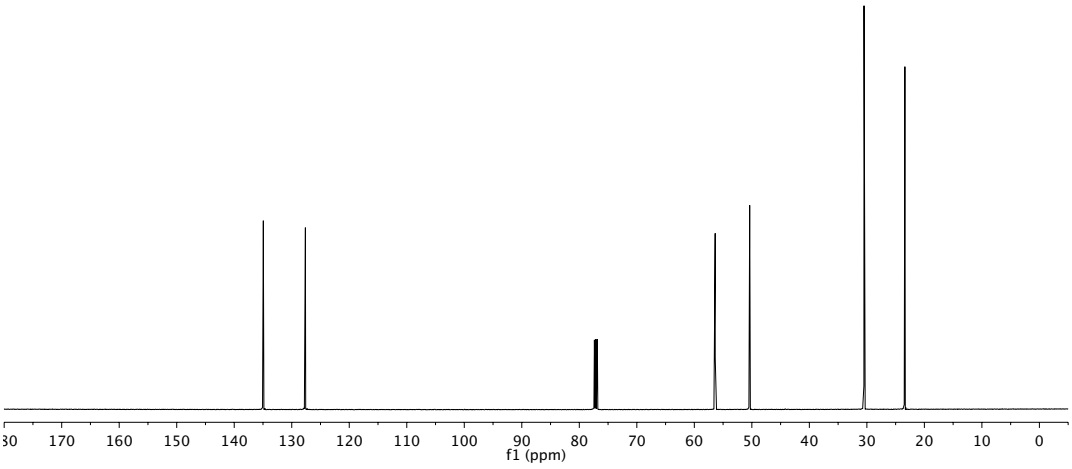




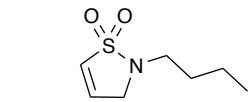
2-Cyclopentyl-2,3-dihydroisothiazole 1,1-dioxide (3.62)

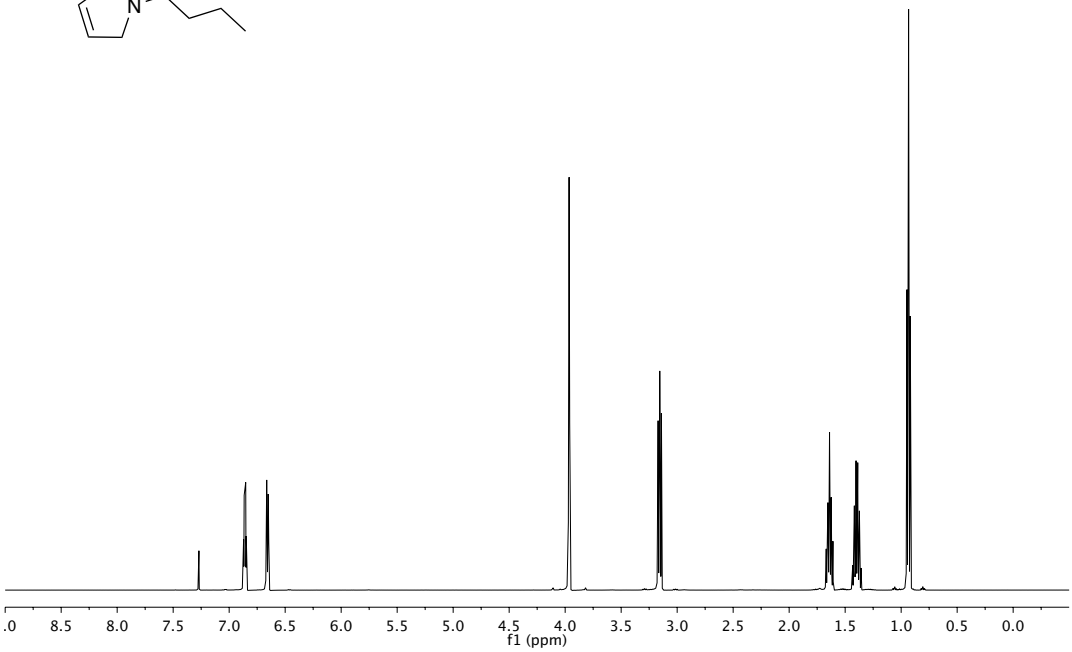


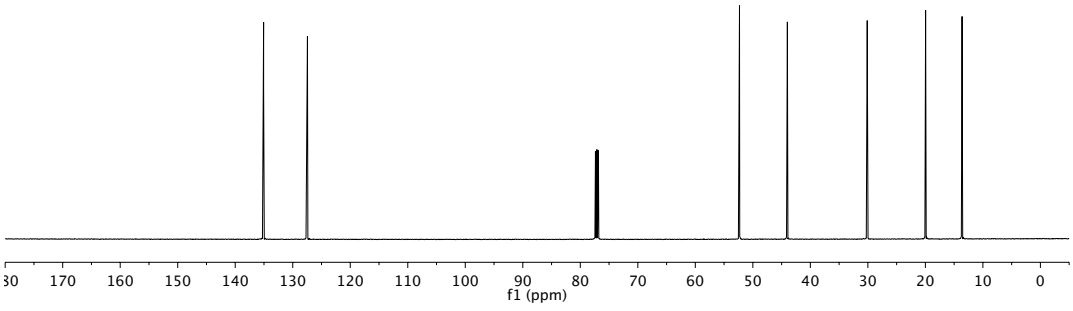




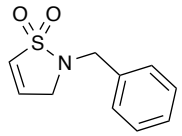
2-Butyl-2,3-dihydroisothiazole 1,1-dioxide (3.63)

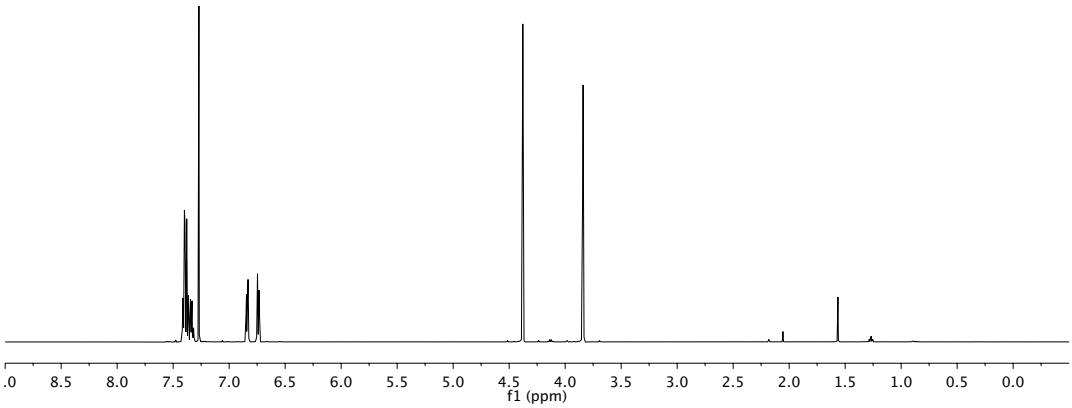


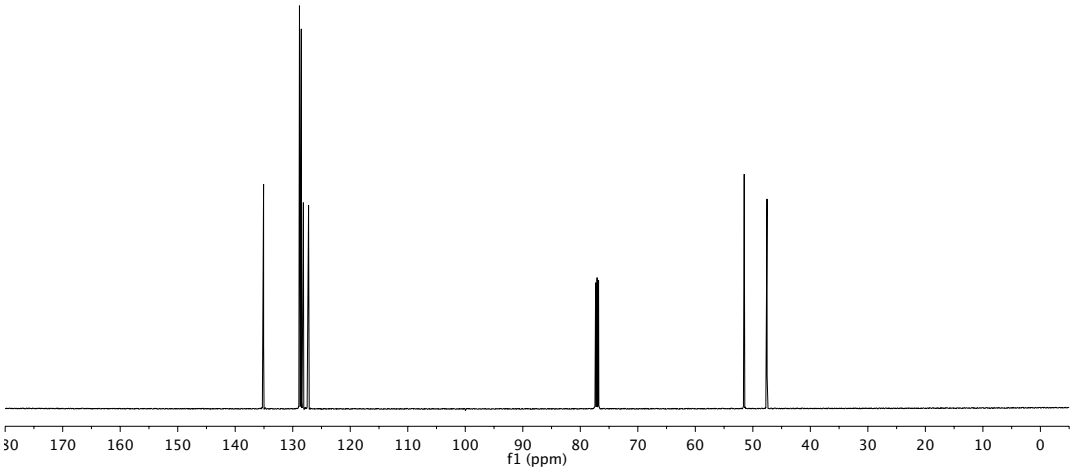




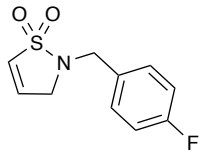
2-Benzyl-2,3-dihydroisothiazole 1,1-dioxide (3.64)

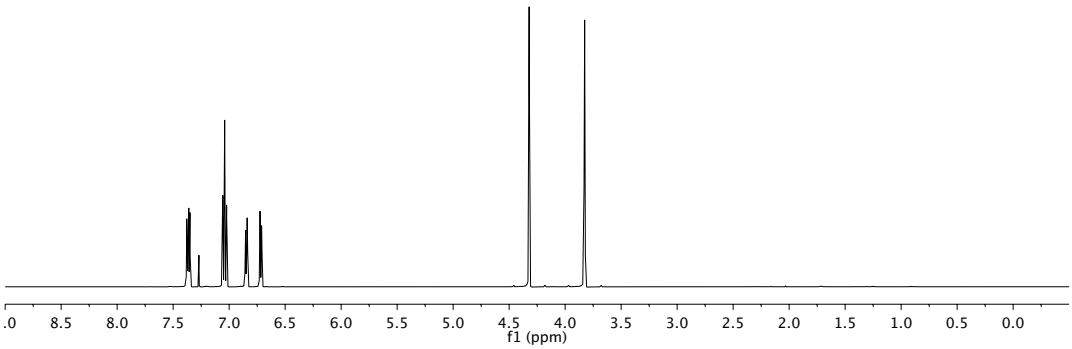


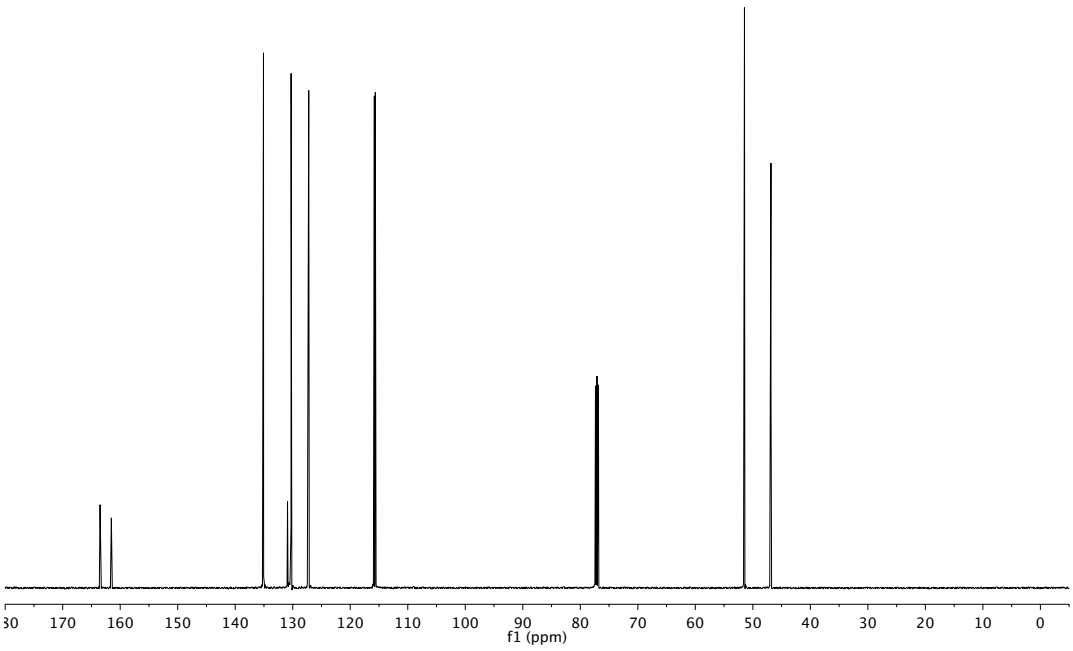




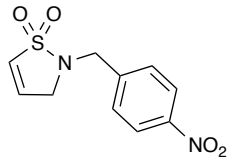
2-(4-Fluorobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.65)

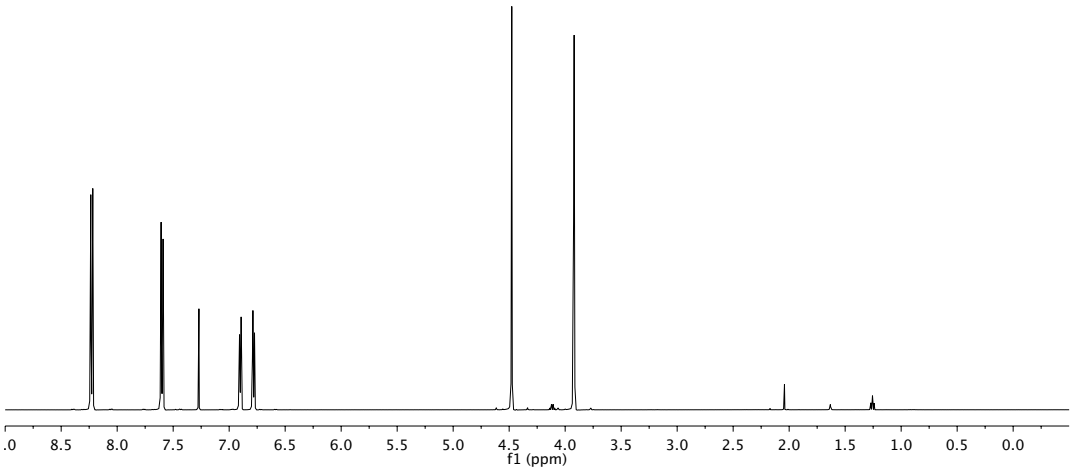


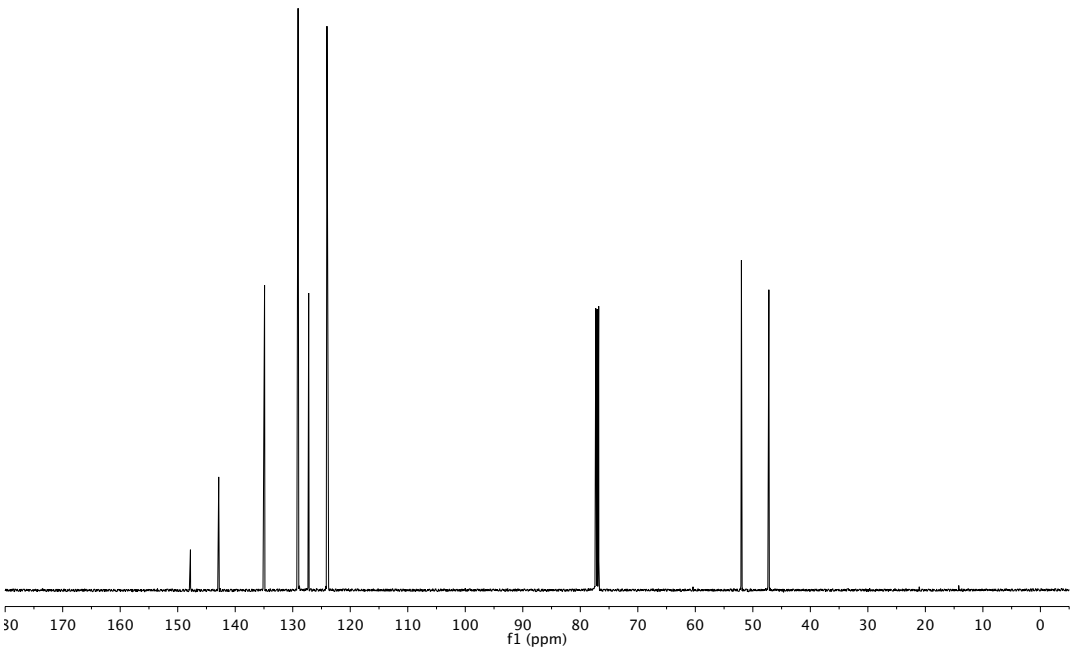




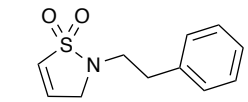
2-(4-Nitrobenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.66)

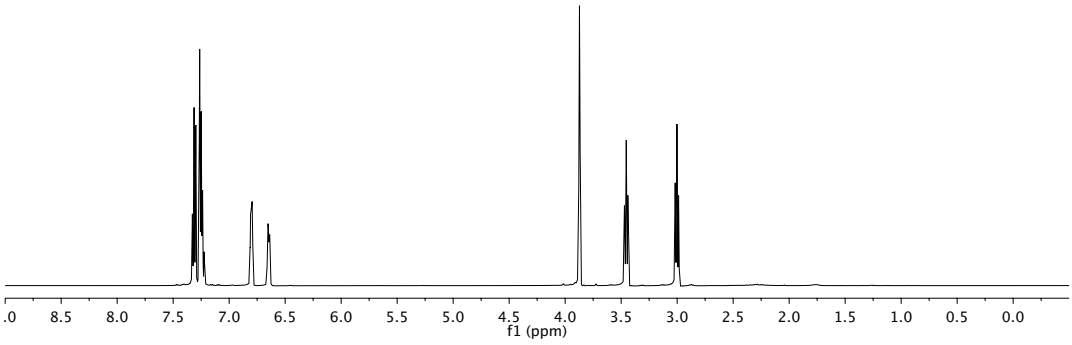


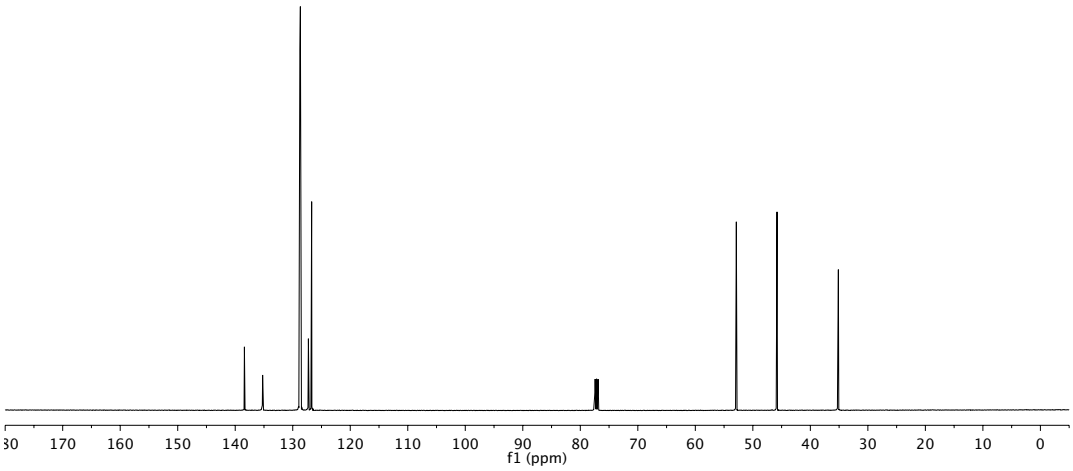




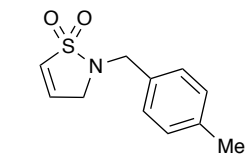
2-Phenethyl-2,3-dihydroisothiazole 1,1-dioxide (3.67)

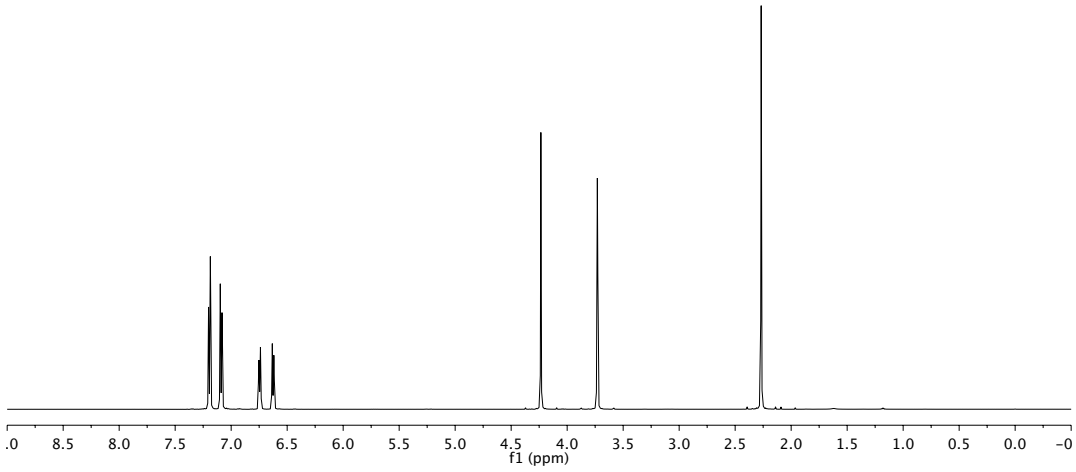


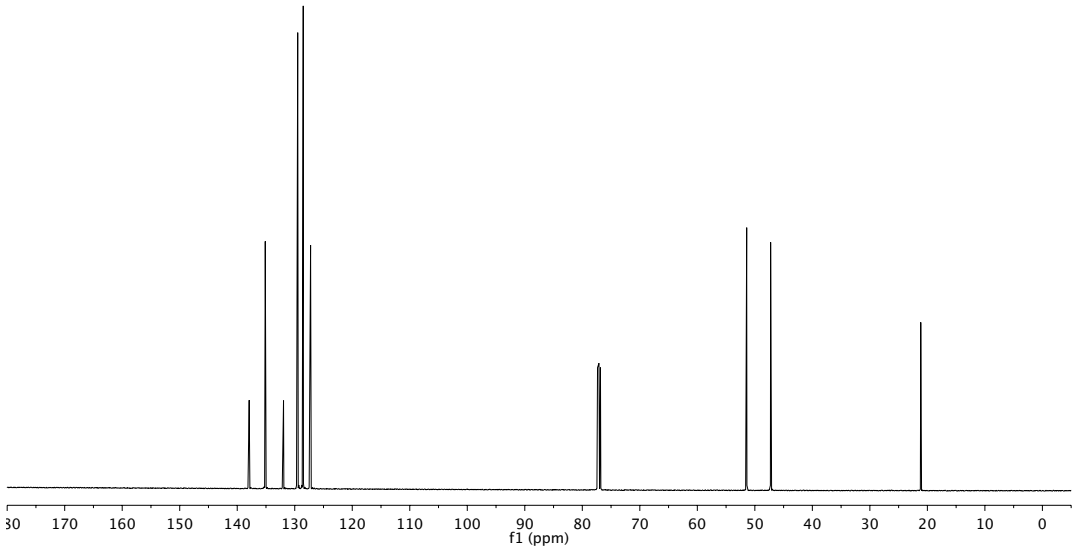




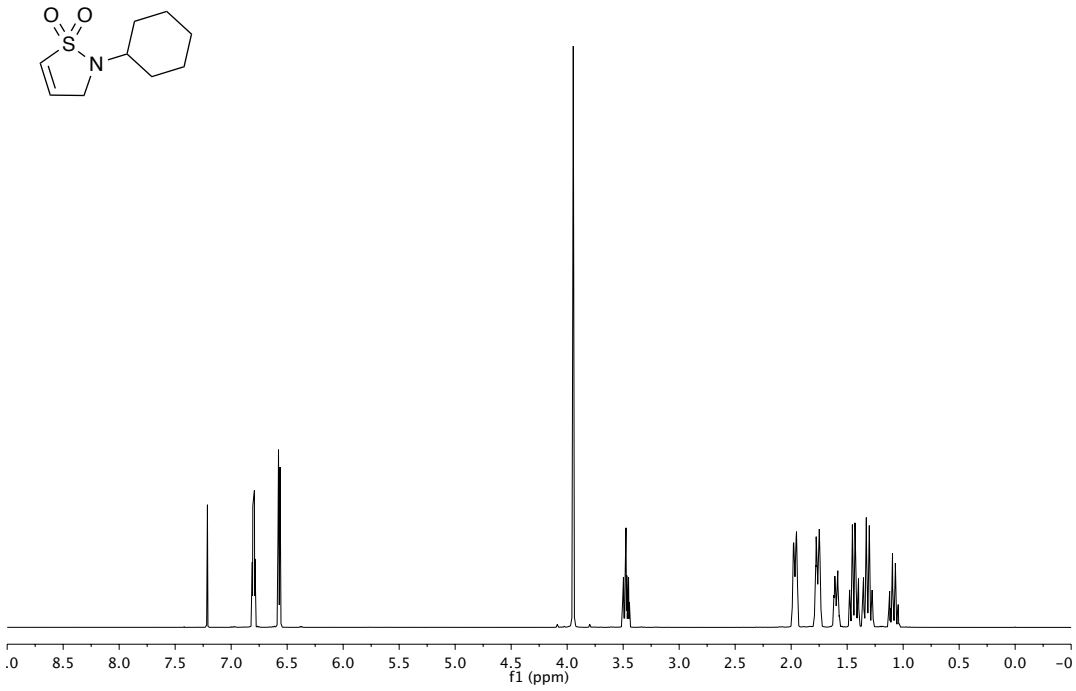
2-(4-Methylbenzyl)-2,3-dihydroisothiazole 1,1-dioxide (3.68)

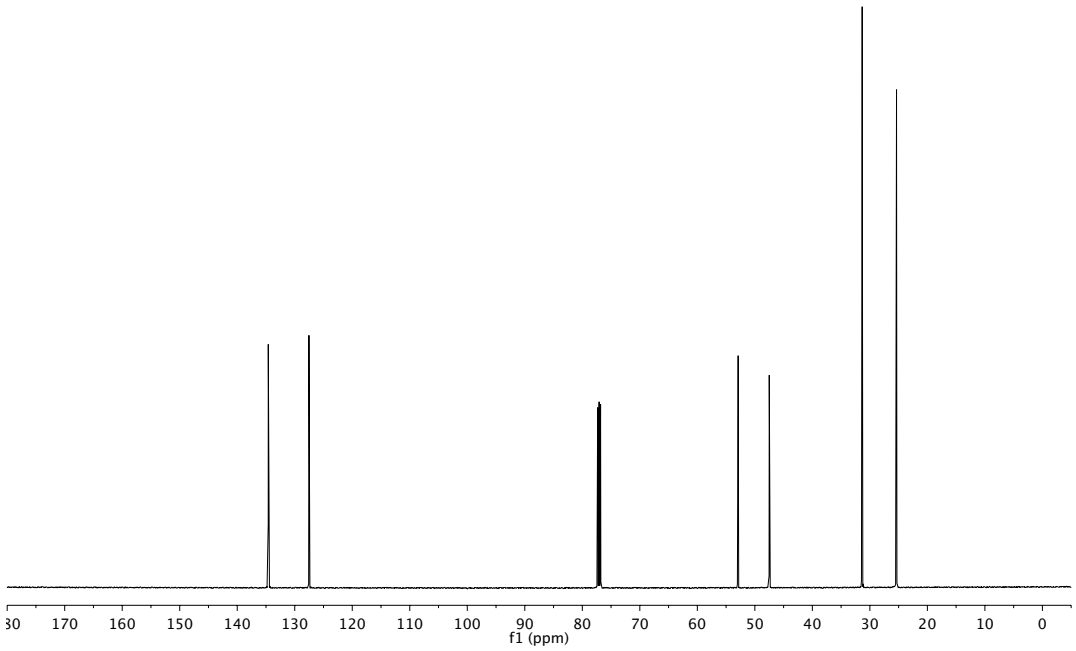




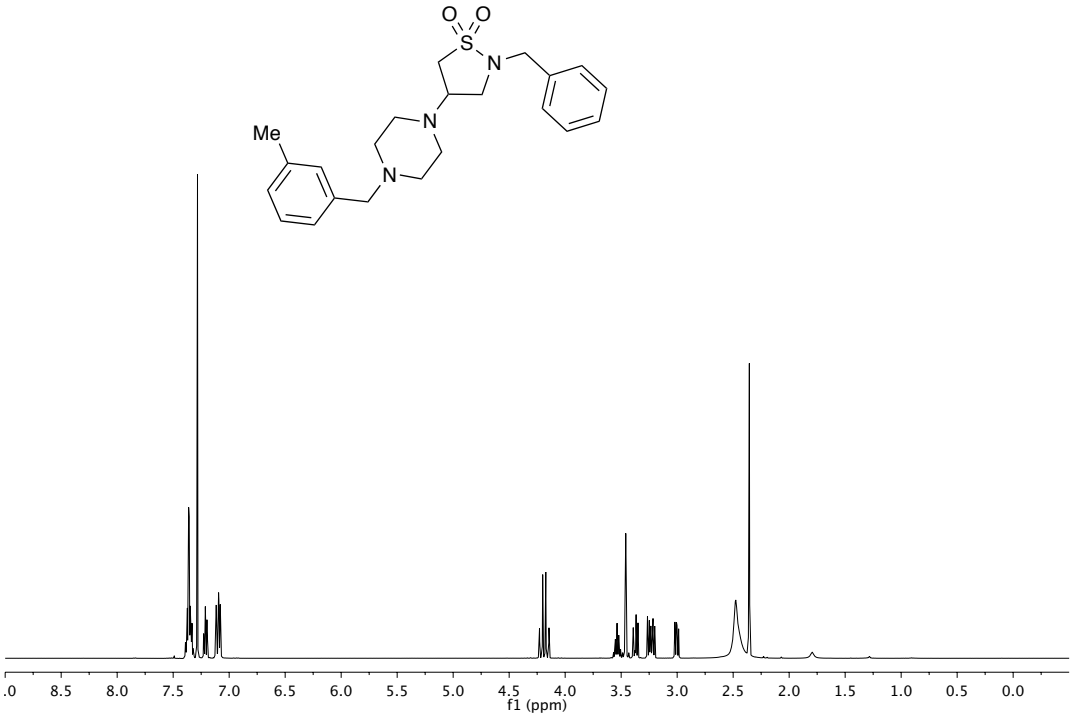


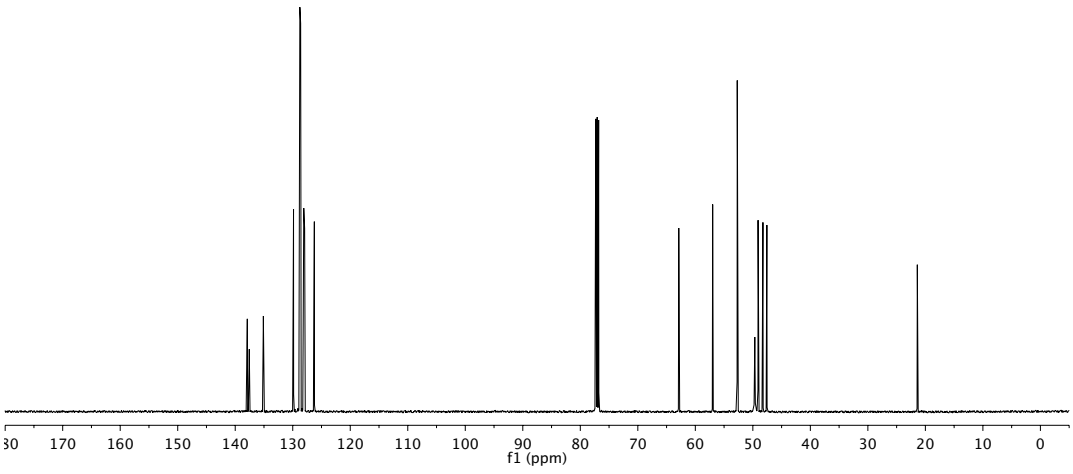
2-Cyclohexyl-2,3-dihydroisothiazole 1,1-dioxide (3.69)



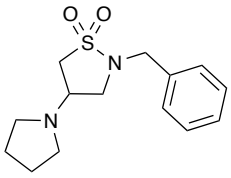


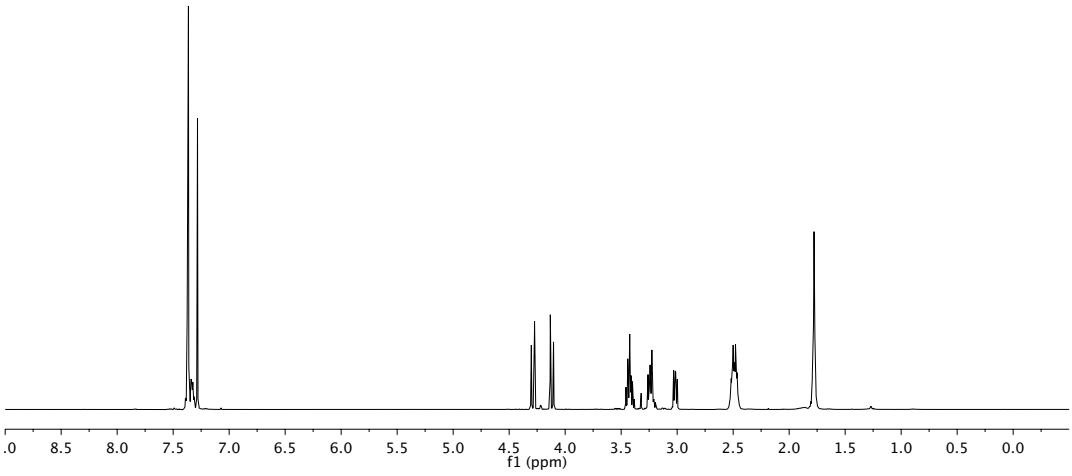
2-Benzyl-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 3.64{4}

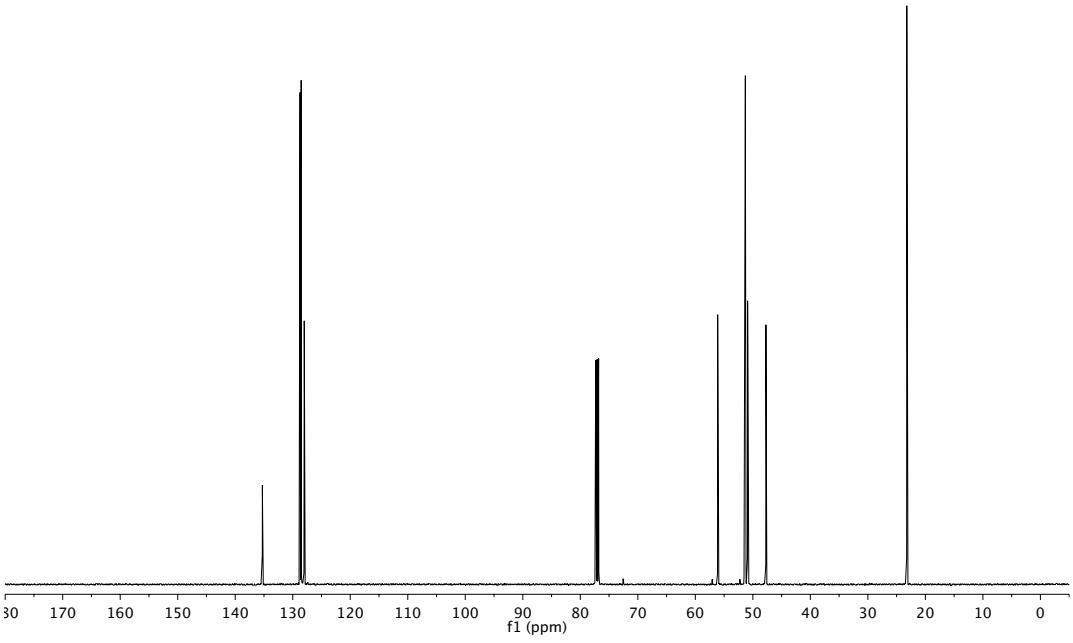




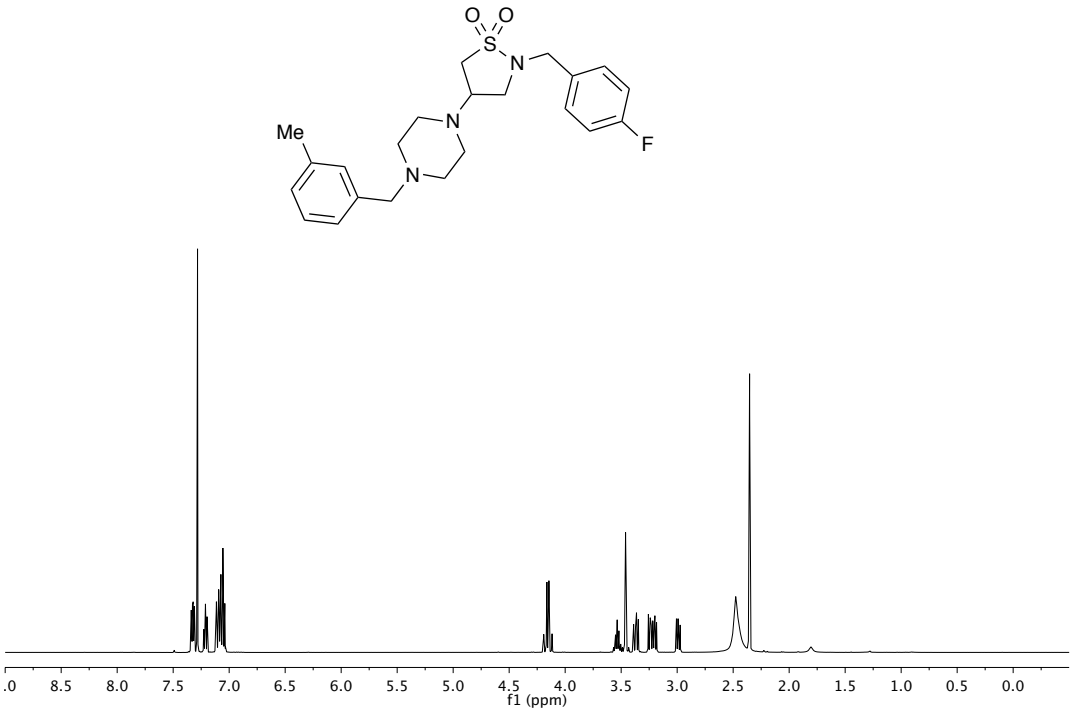
2-Benzyl-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.64{16}

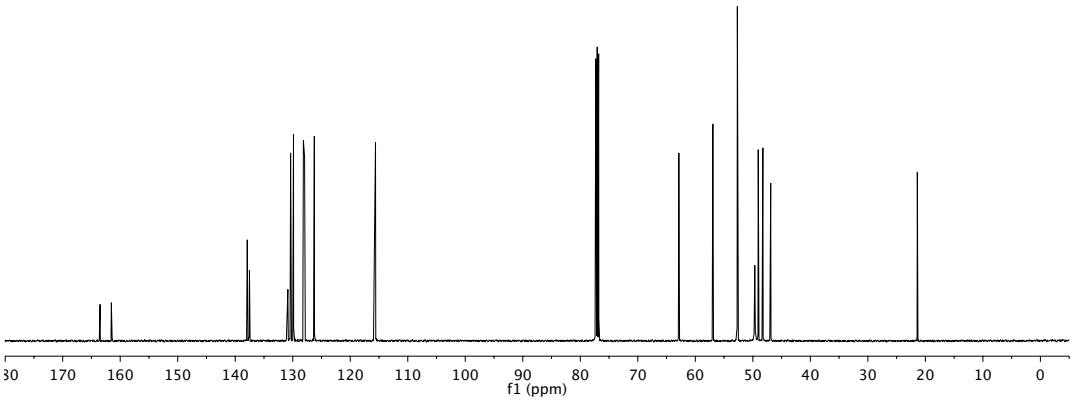




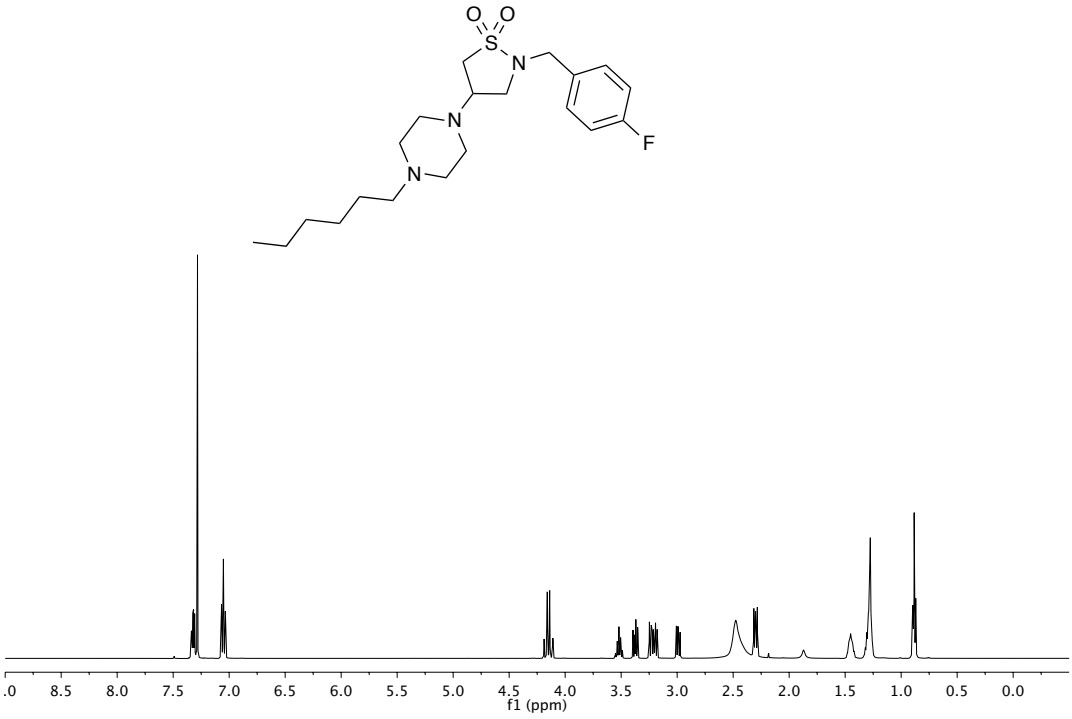


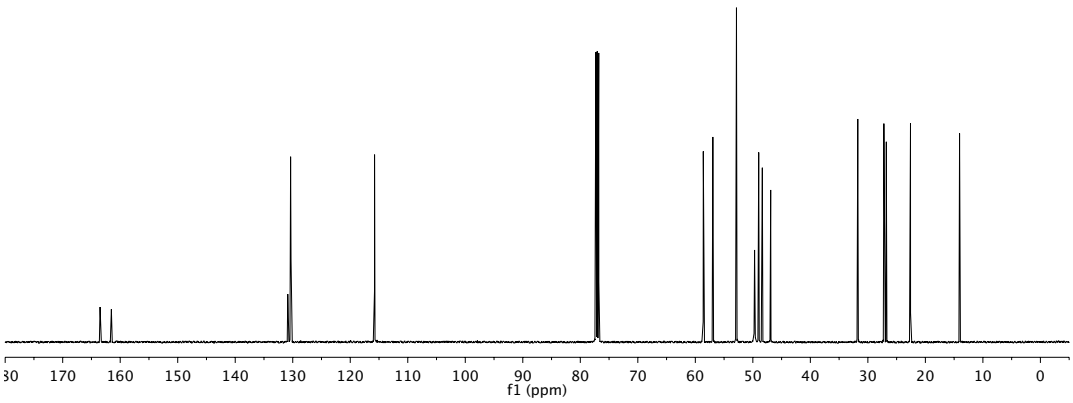
2-(4-Fluorobenzyl)-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 3.65{4}



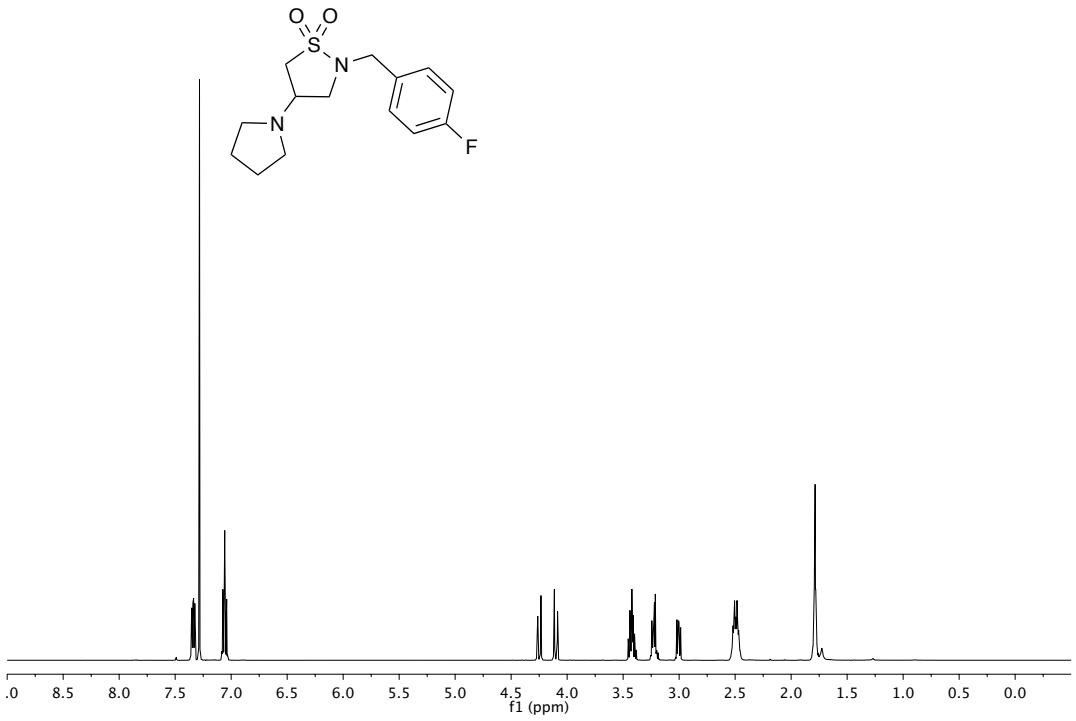


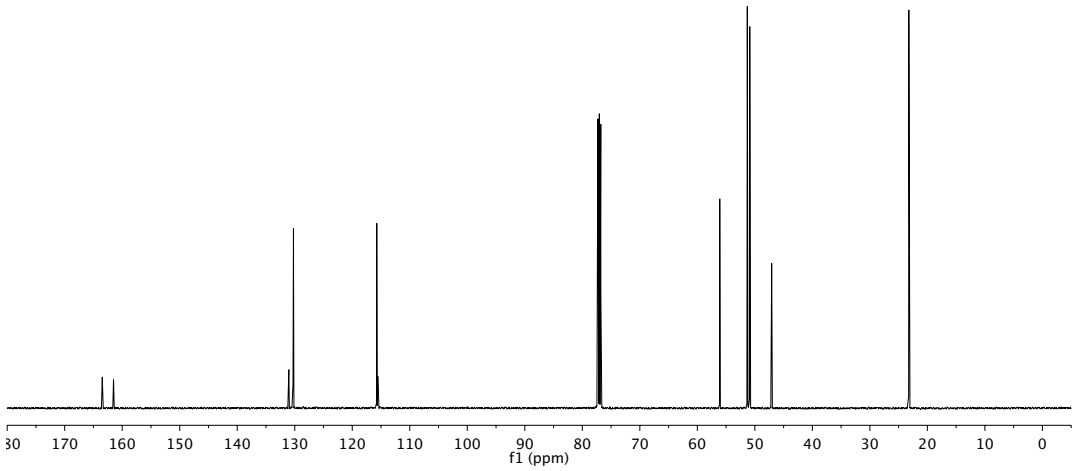
2-(4-Fluorobenzyl)-4-(4-hexylpiperazin-1-yl)isothiazolidine 1,1-dioxide 3.65{7}



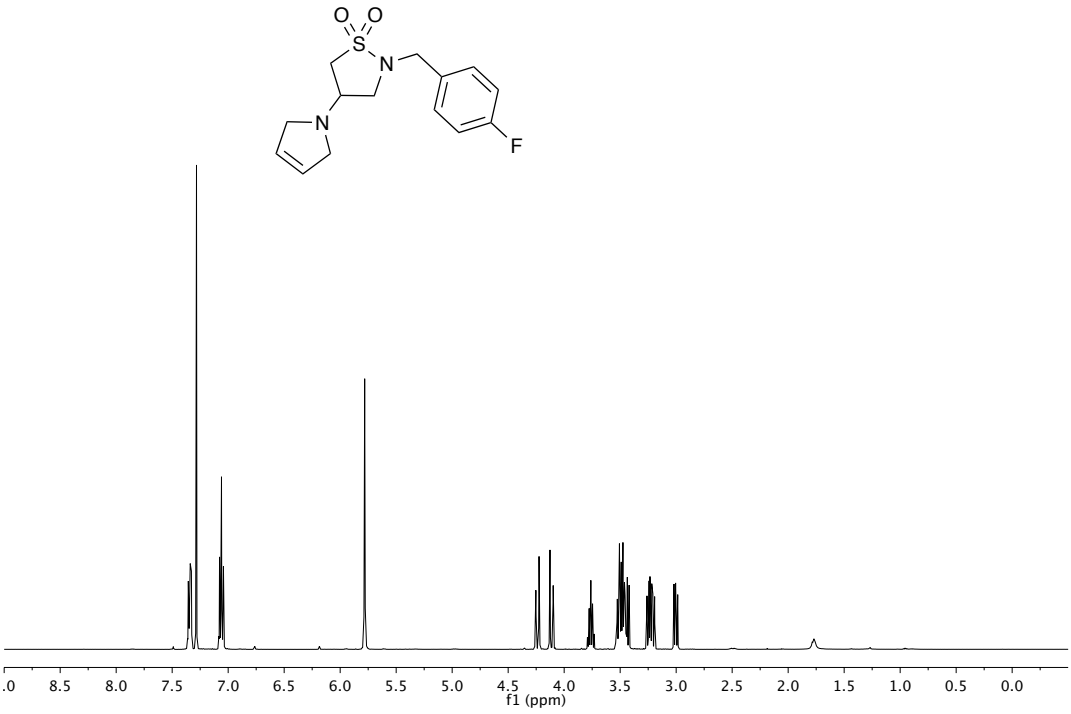


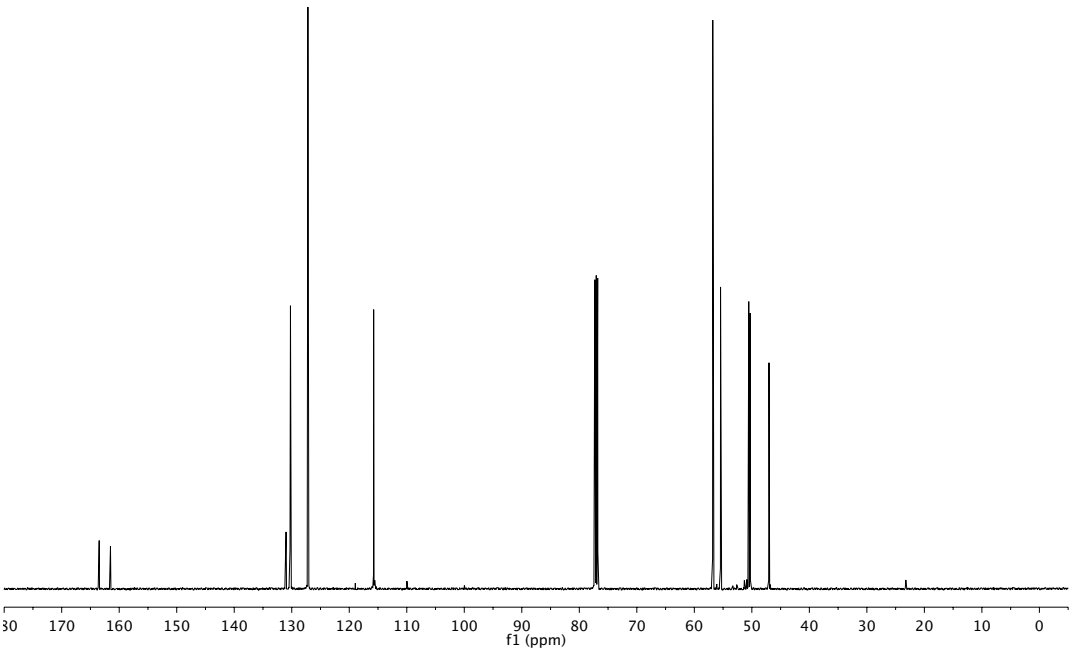
2-(4-Fluorobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.65{16}



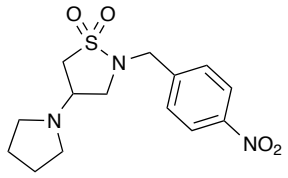


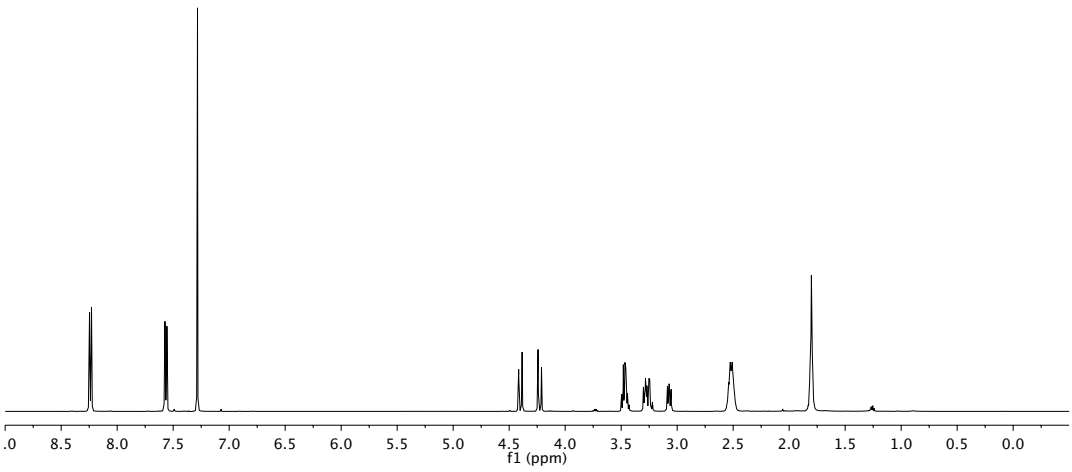
4-(2,5-Dihydro-1*H*-pyrrol-1-yl)-2-(4-fluorobenzyl)isothiazolidine 1,1-dioxide 3.65{17}

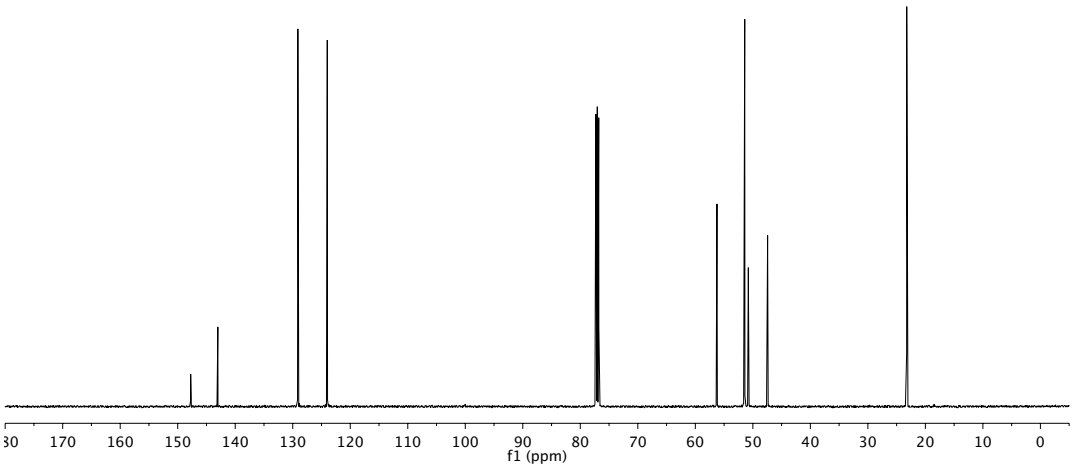




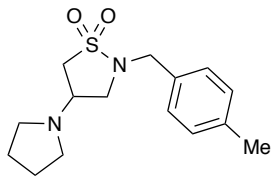
2-(4-Nitrobenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.66{16}

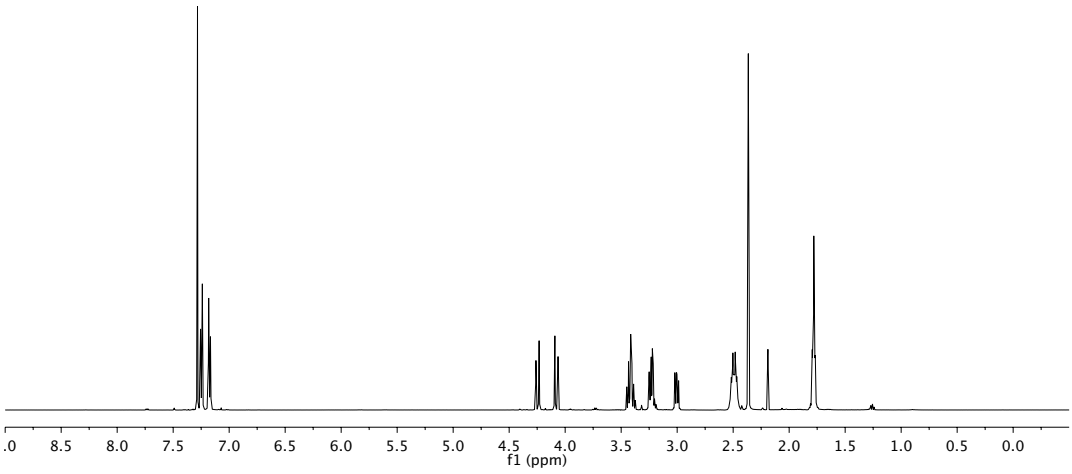


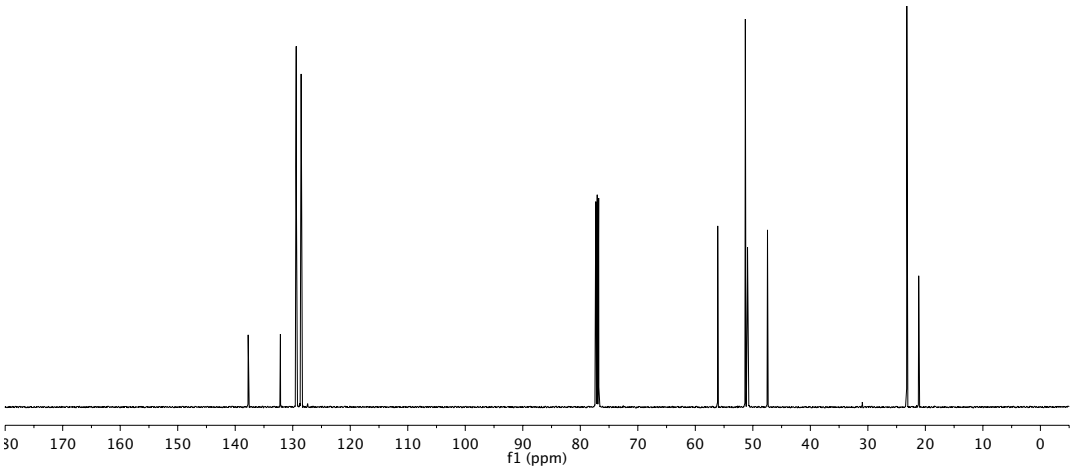




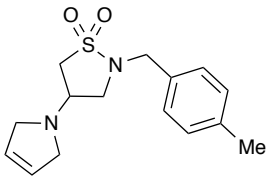
2-(4-Methylbenzyl)-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.68{16}

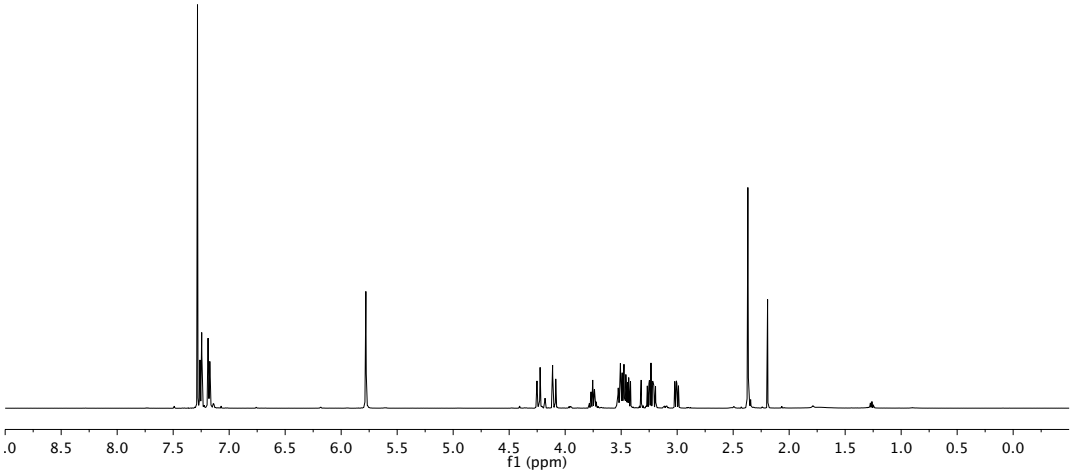


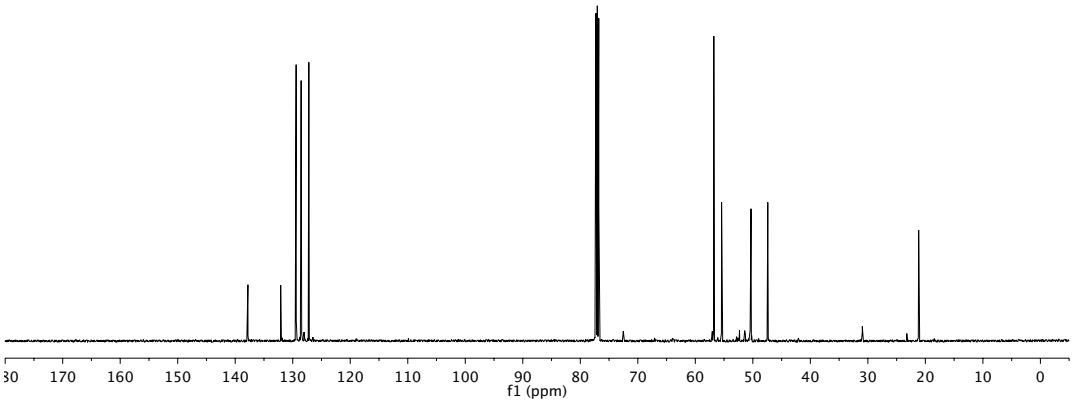




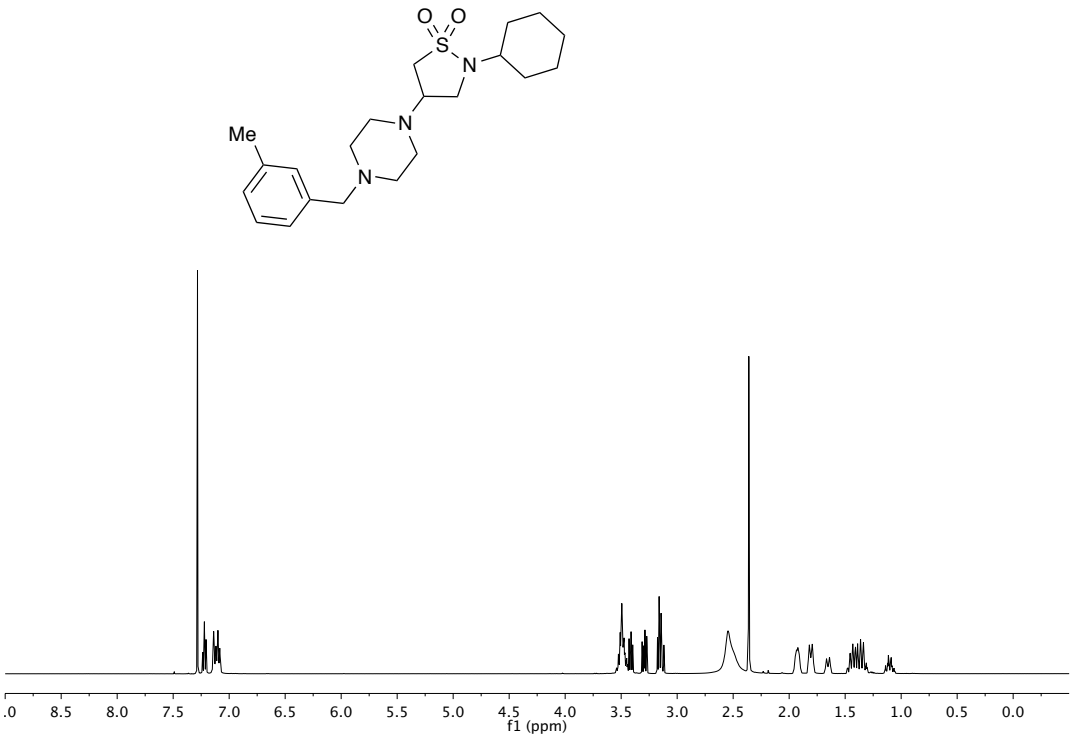
4-(2,5-Dihydro-1*H*-pyrrol-1-yl)-2-(4-methylbenzyl)isothiazolidine 1,1-dioxide 3.68{17}



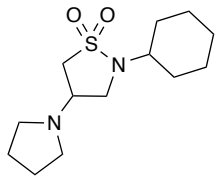


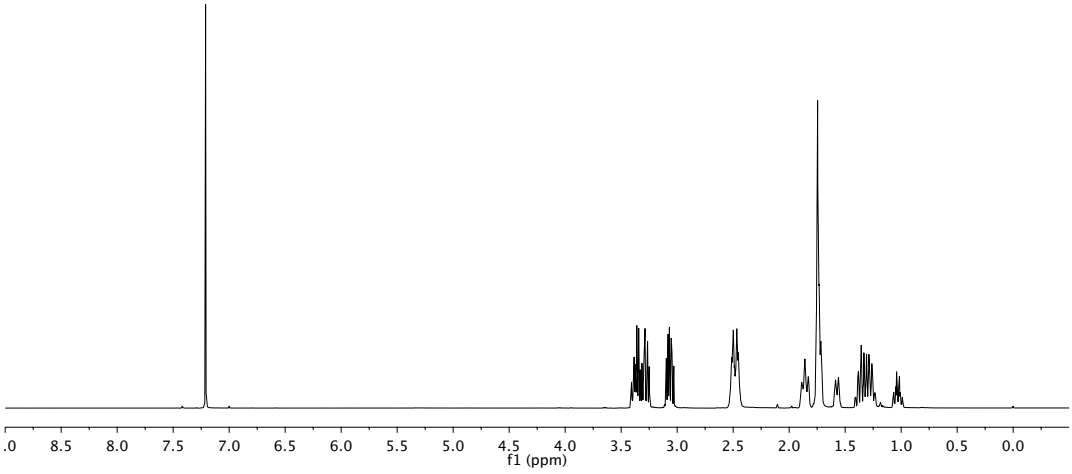


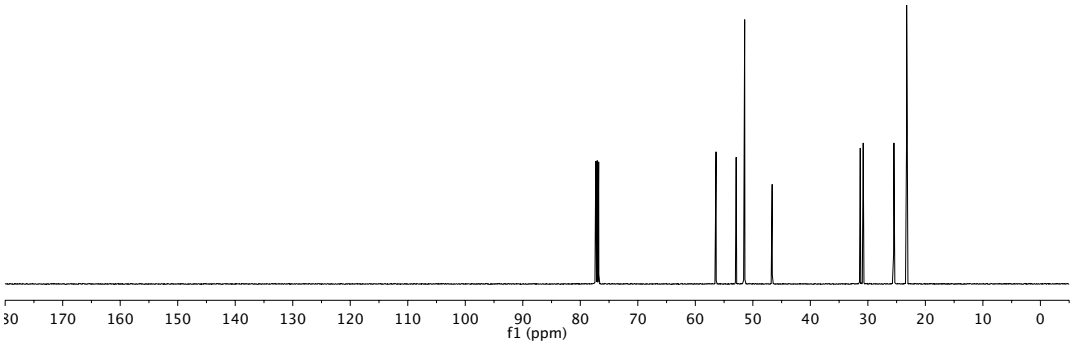
2-Cyclohexyl-4-(4-(3-methylbenzyl)piperazin-1-yl)isothiazolidine 1,1-dioxide 3.69{4}



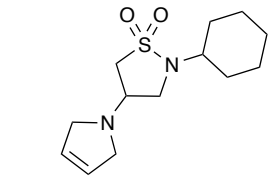
2-Cyclohexyl-4-(pyrrolidin-1-yl)isothiazolidine 1,1-dioxide 3.69{16}

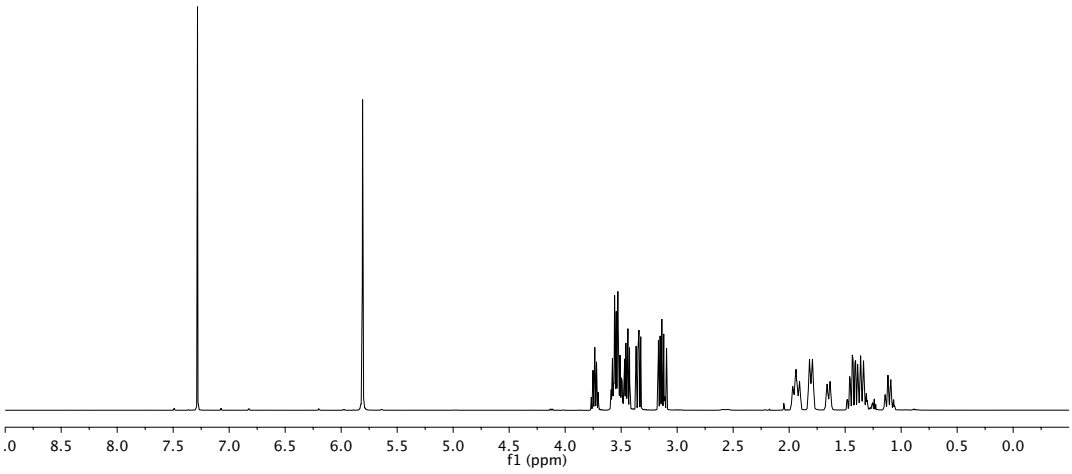


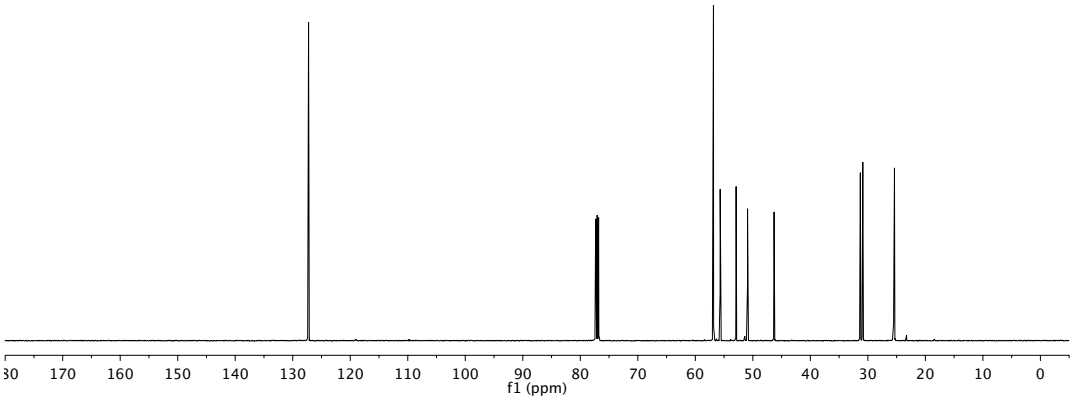




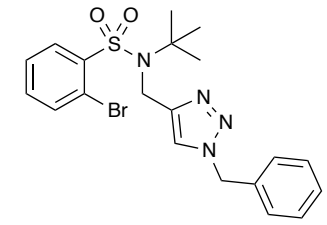
2-Cyclohexyl-4-(2,5-dihydro-1*H*-pyrrol-1-yl)isothiazolidine 1,1-dioxide 3.69{17}

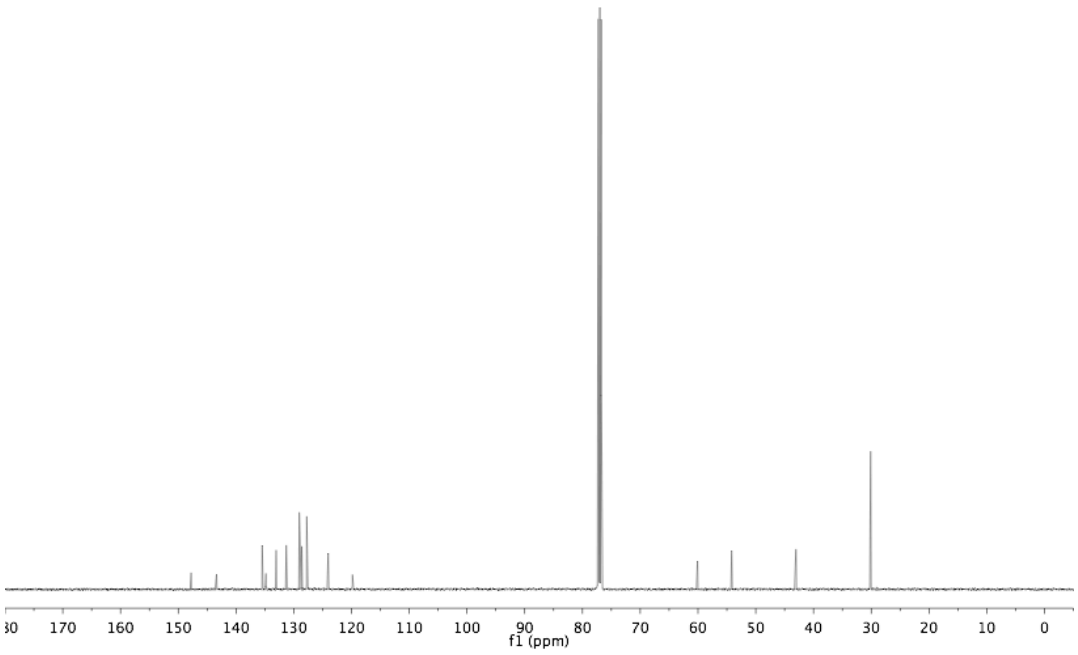




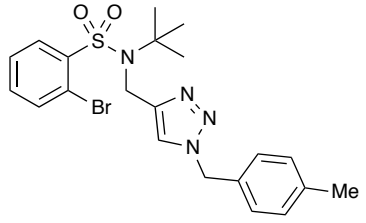


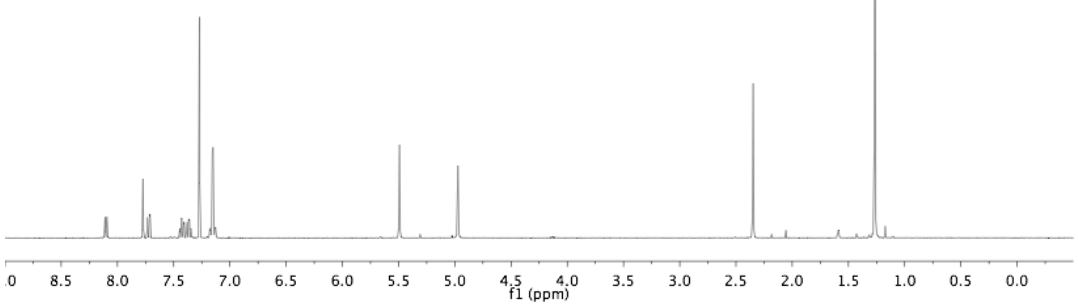
_N_-((1-Benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-2-bromo-_N_-(_tert_ butyl)benzenesulfonamide (4.16)

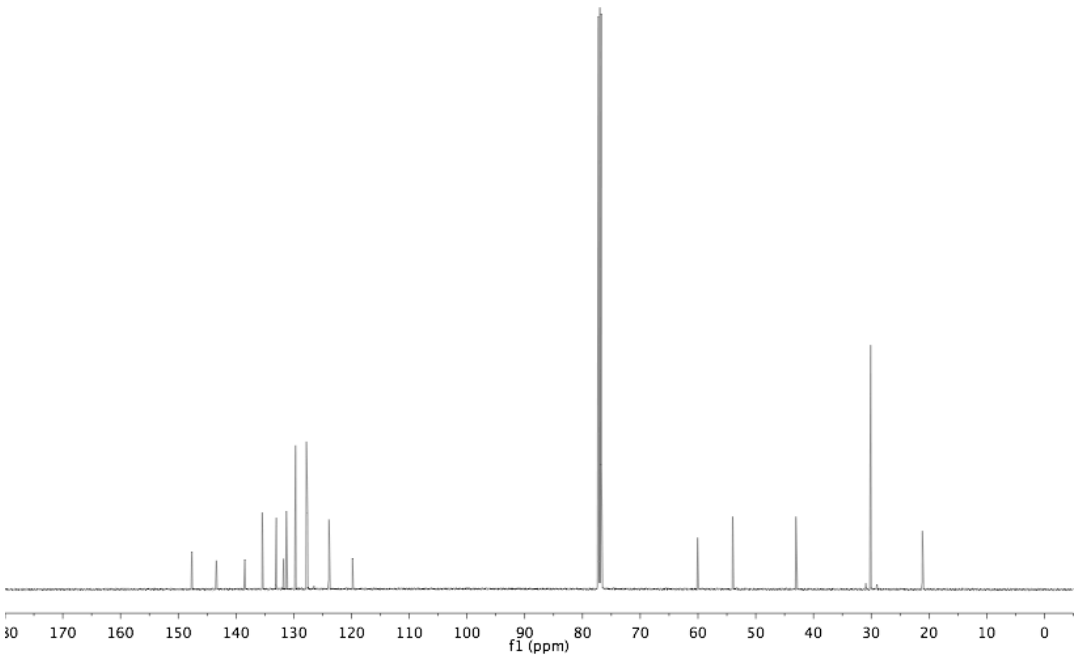




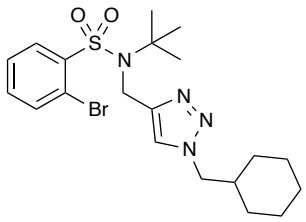
2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.17)

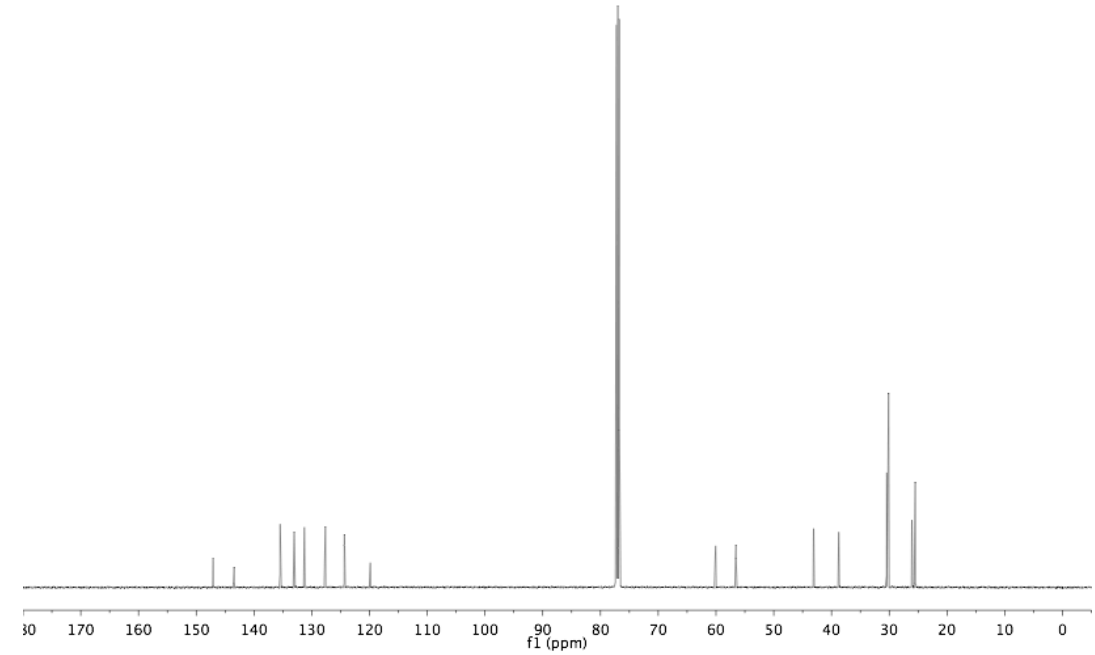




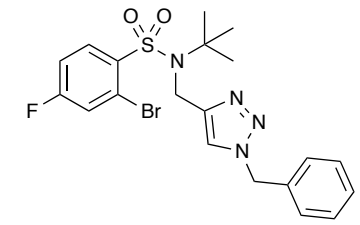


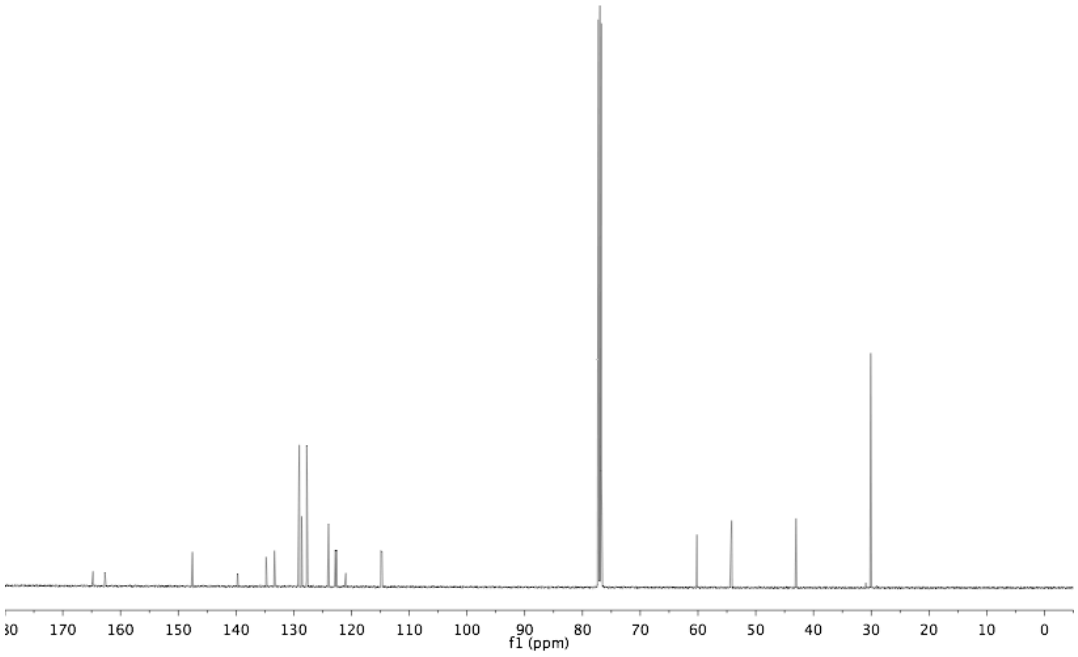
2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.18)



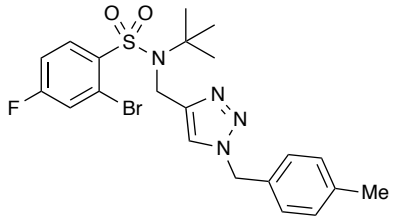


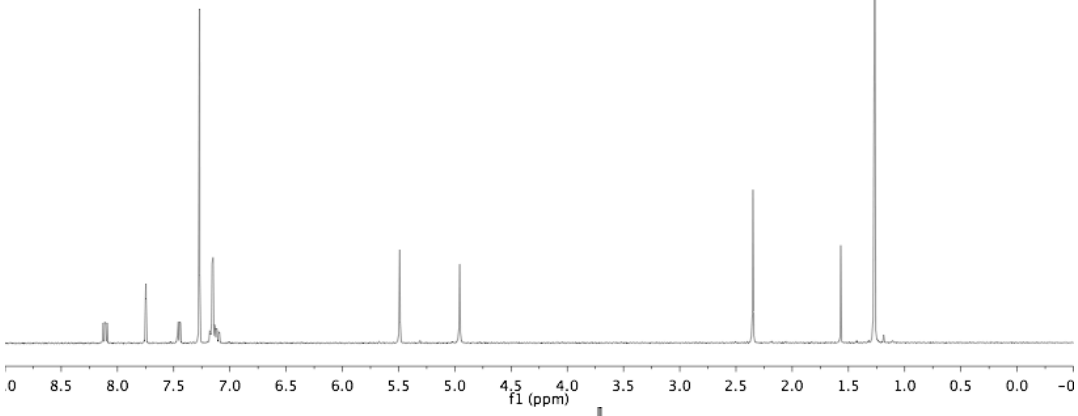
_N_-((1-Benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-2-bromo-_N_-(_tert_-butyl)-4-fluorobenzenesulfonamide (4.19)

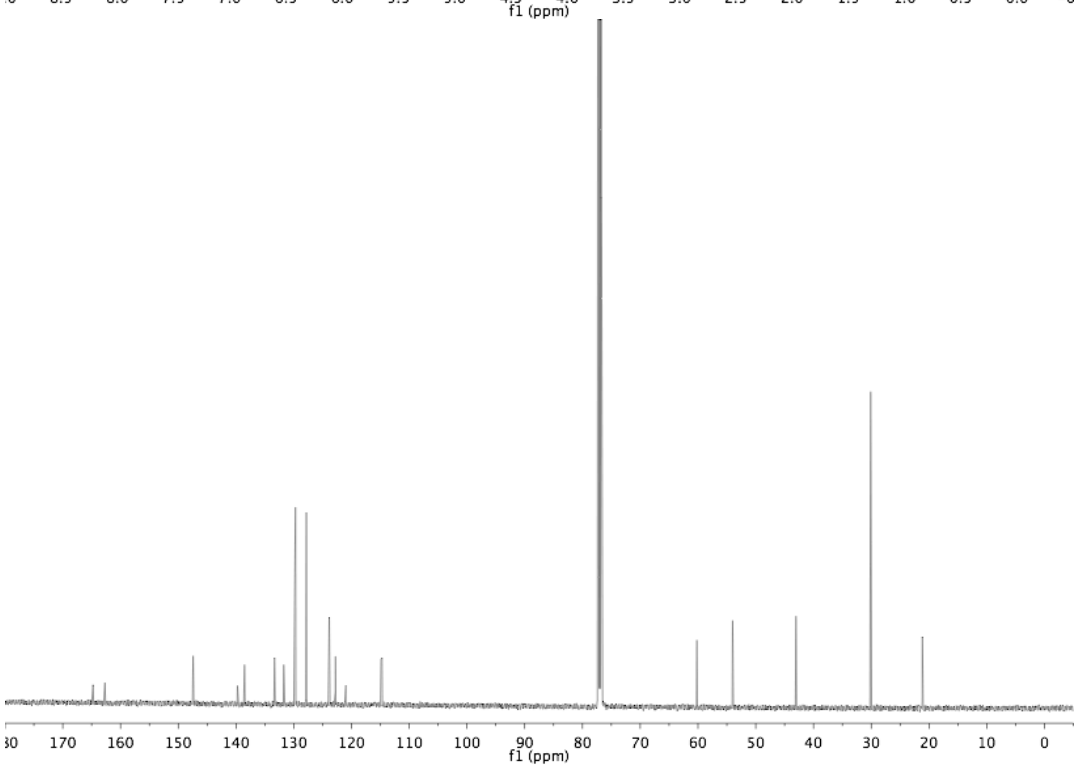




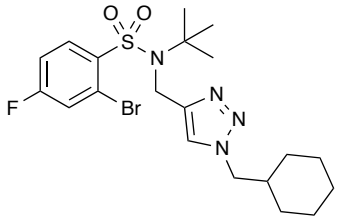
2-Bromo-*N*-(*tert*-butyl)-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (4.20)

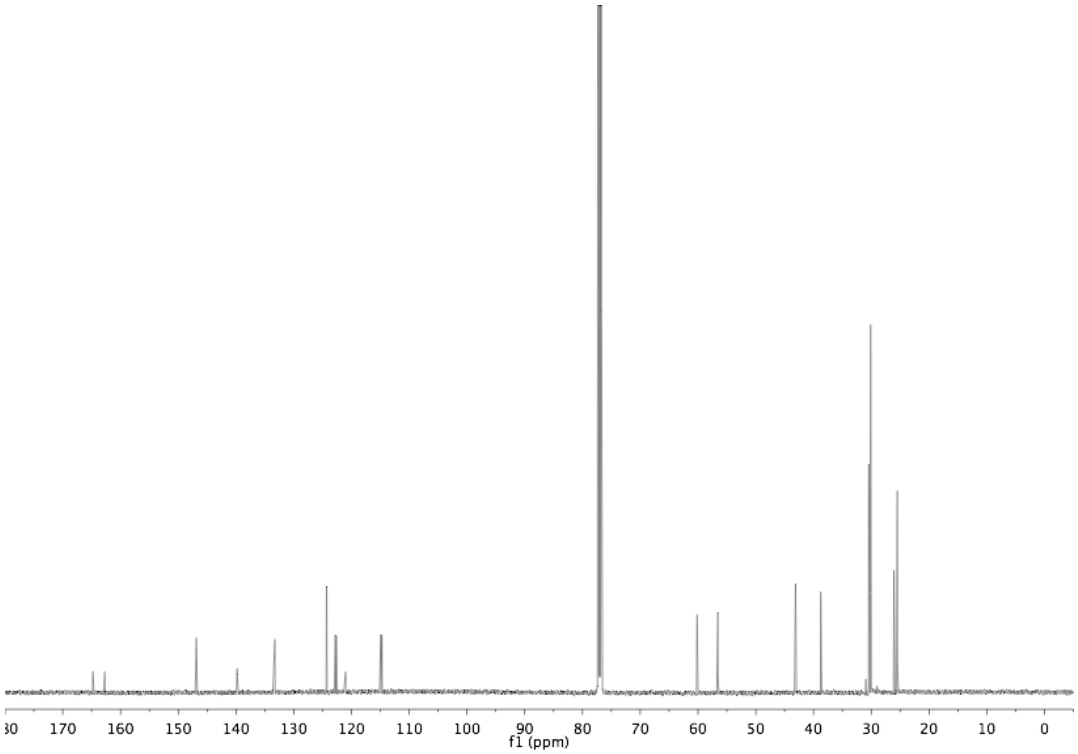




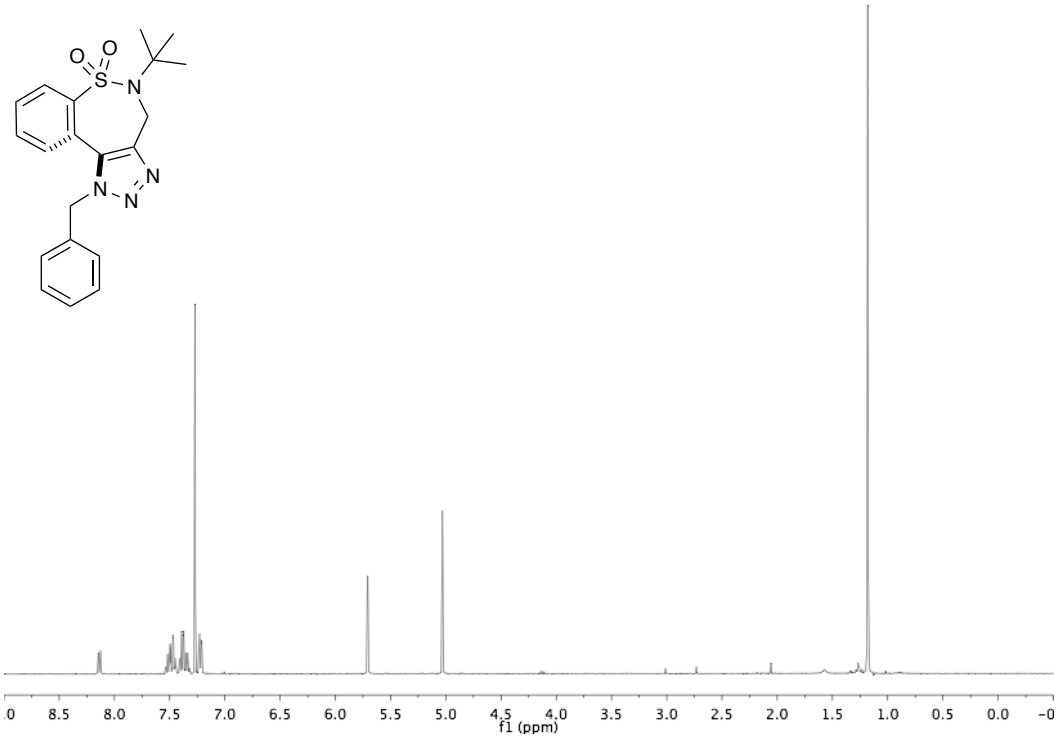


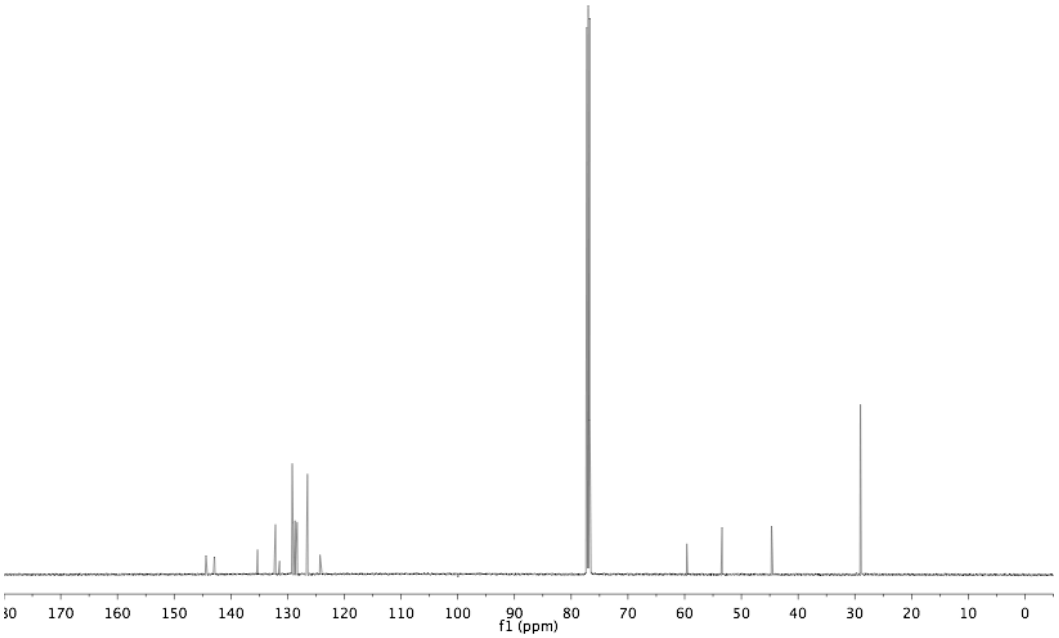
2-Bromo-*N*-(*tert*-butyl)-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorobenzenesulfonamide (4.21)



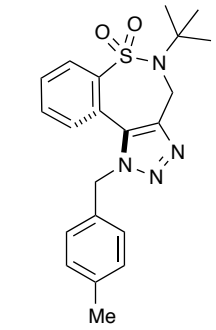


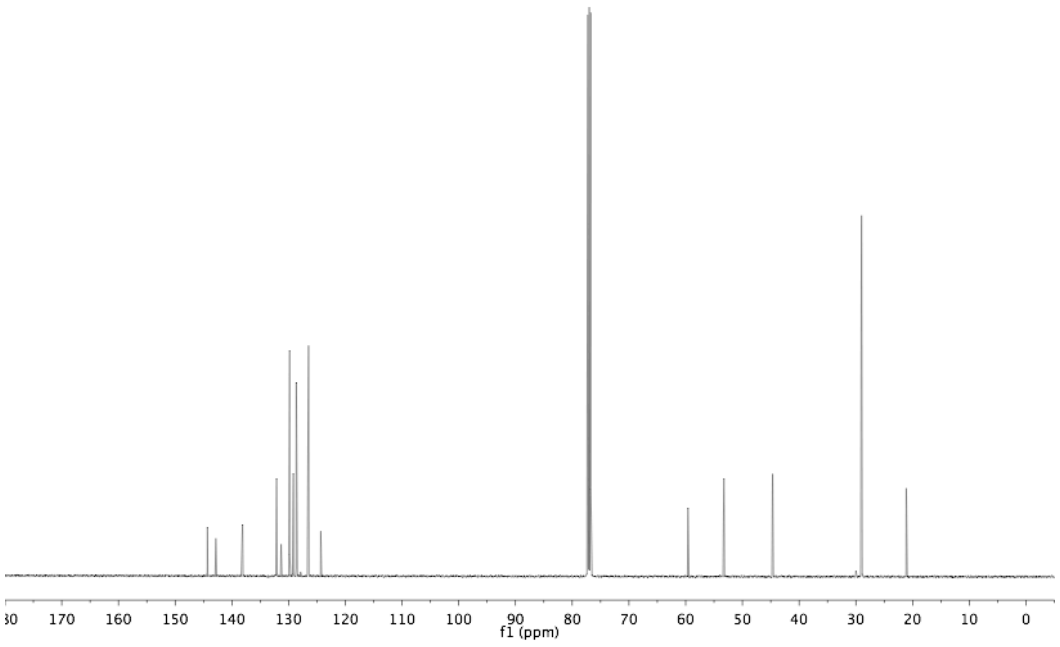
(±)-1-Benzyl-5-(*tert*-butyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.22)



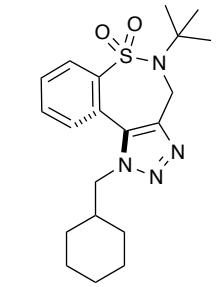


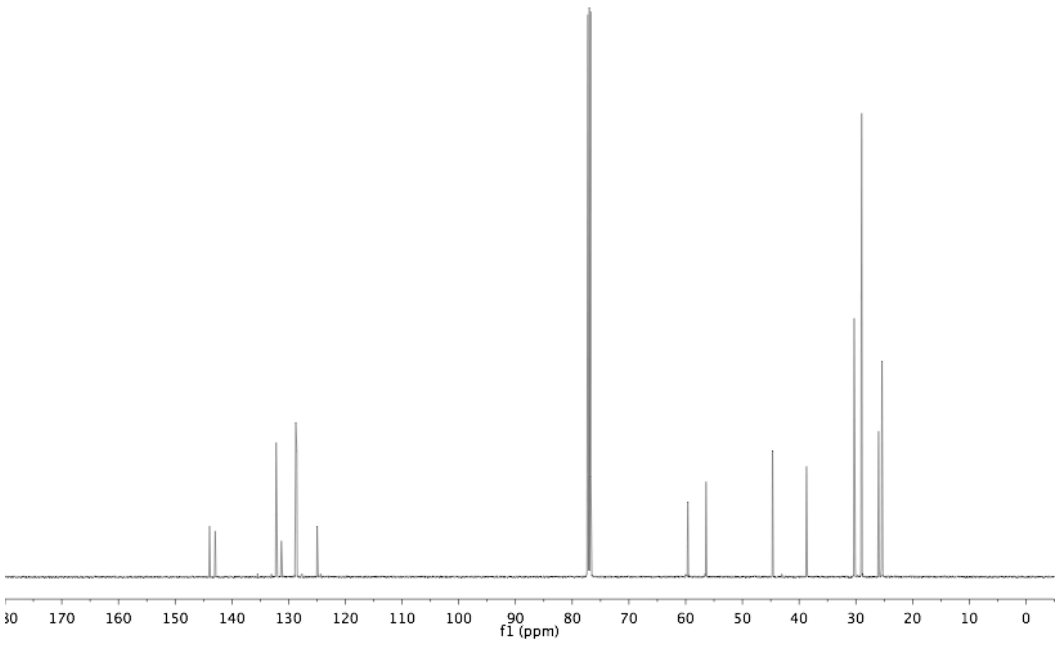
(±)-5-(*tert*-Butyl)-1-(4-methylbenzyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.23)



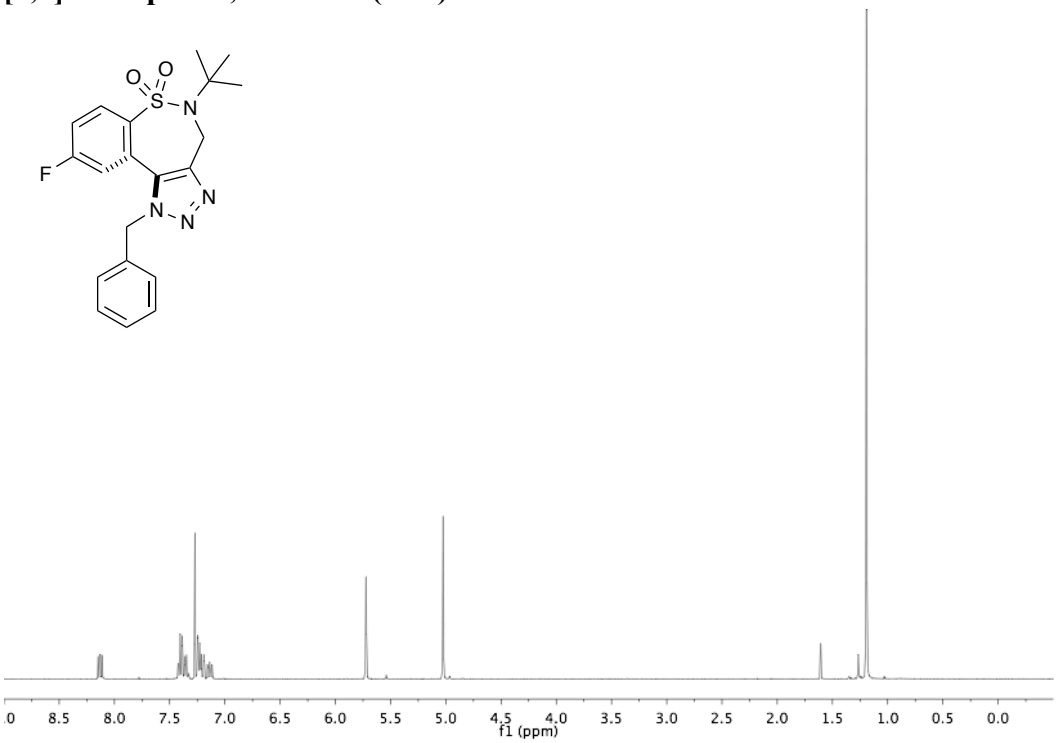


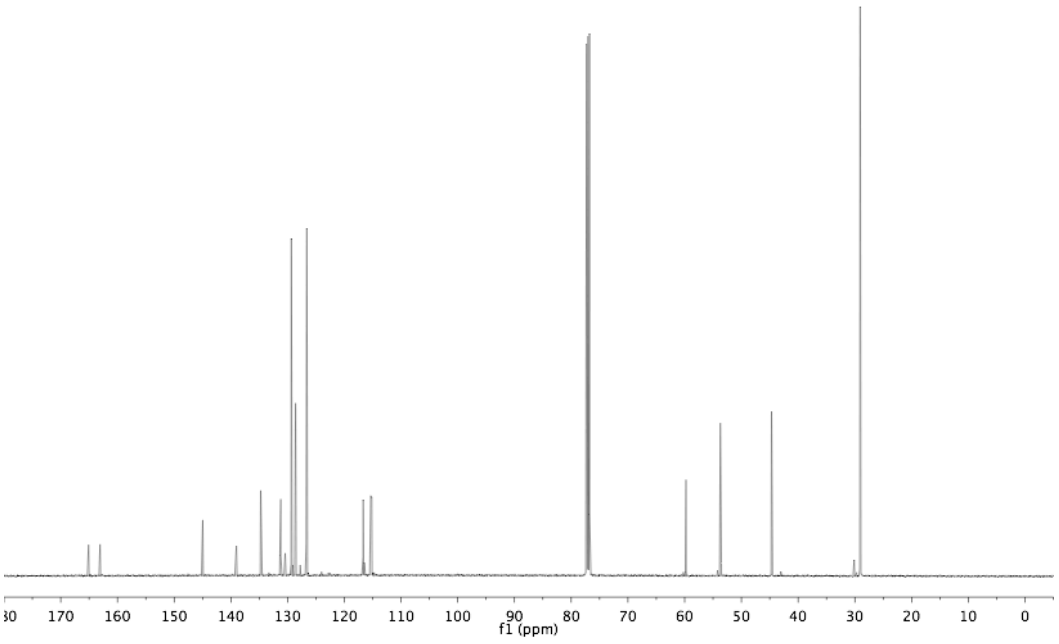
(±)-5-(*tert*-Butyl)-1-(cyclohexylmethyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.24)



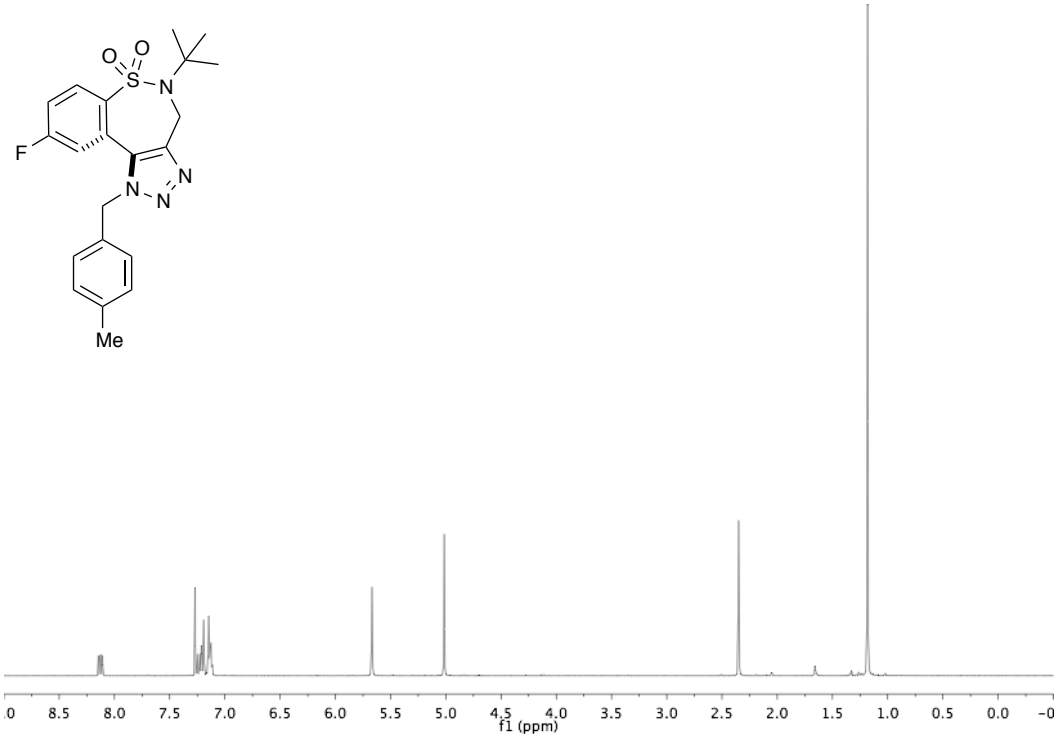


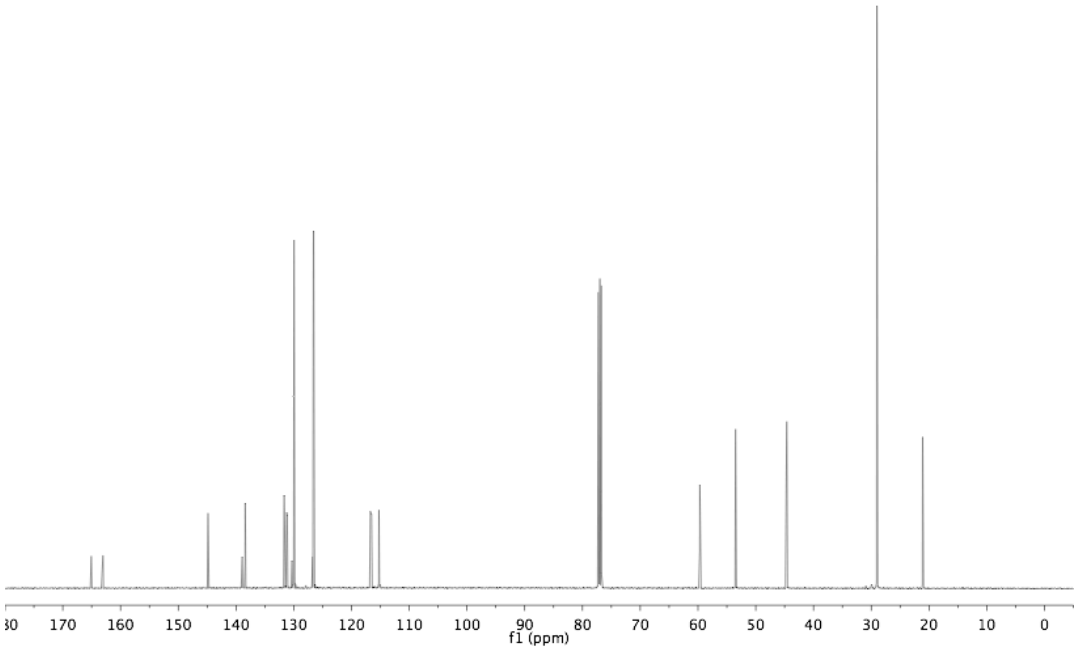
(±)-1-Benzyl-5-(*tert*-butyl)-9-fluoro-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.25)



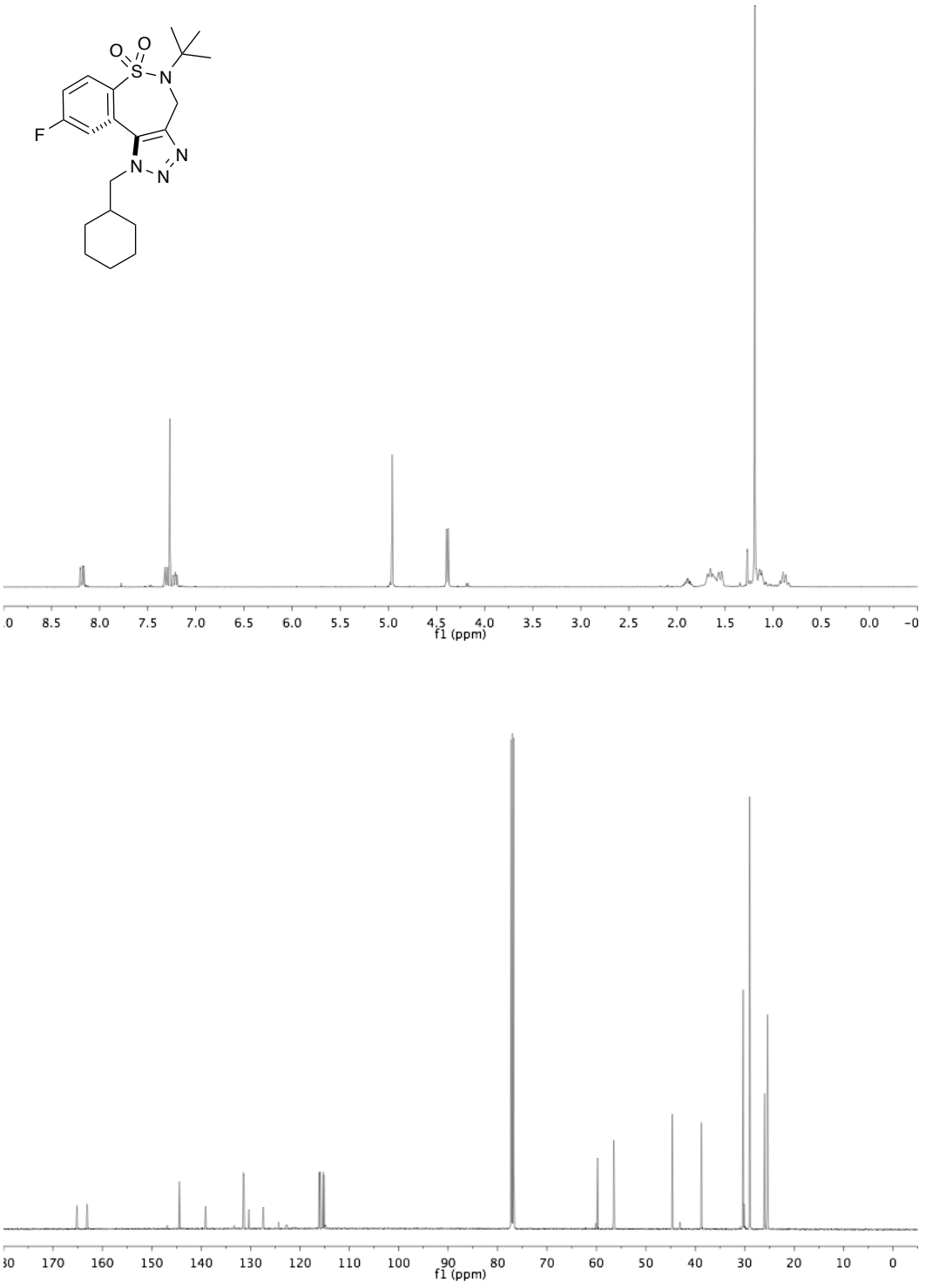


(±)-5-(*tert*-Butyl)-9-fluoro-1-(4-methylbenzyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.26)

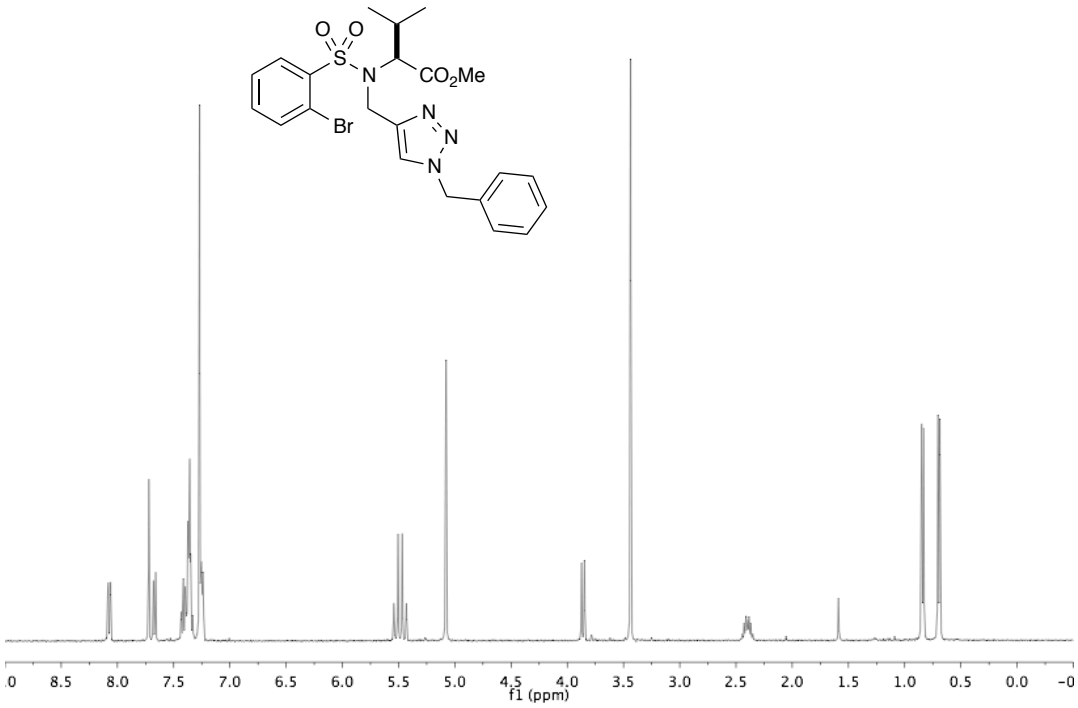


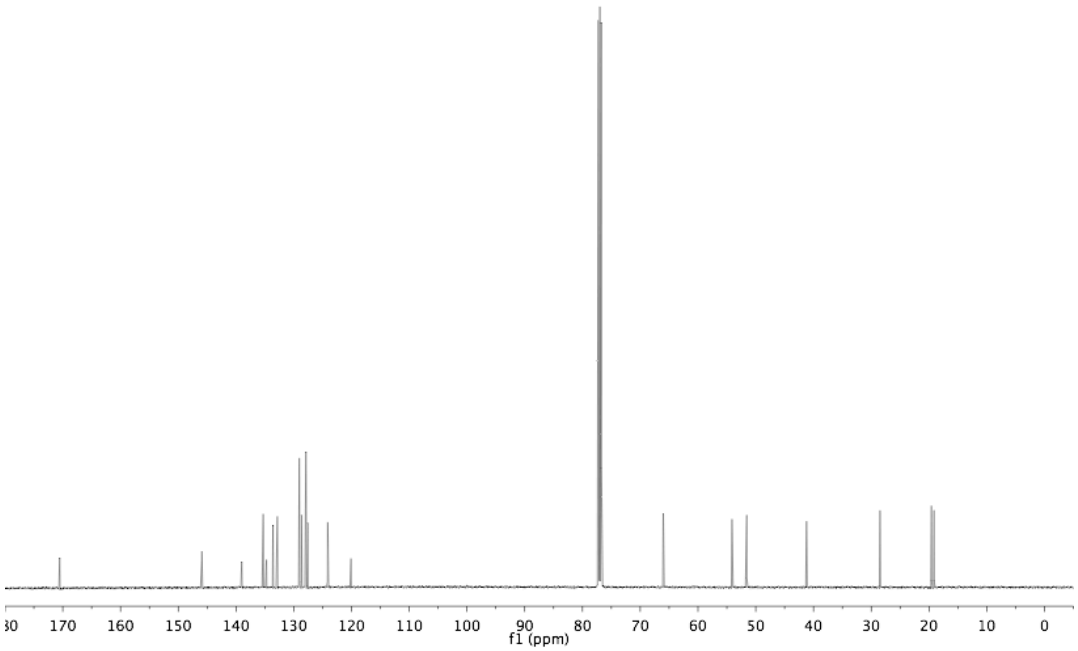


(±)-5-(*tert*-Butyl)-1-(cyclohexylmethyl)-9-fluoro-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.27)

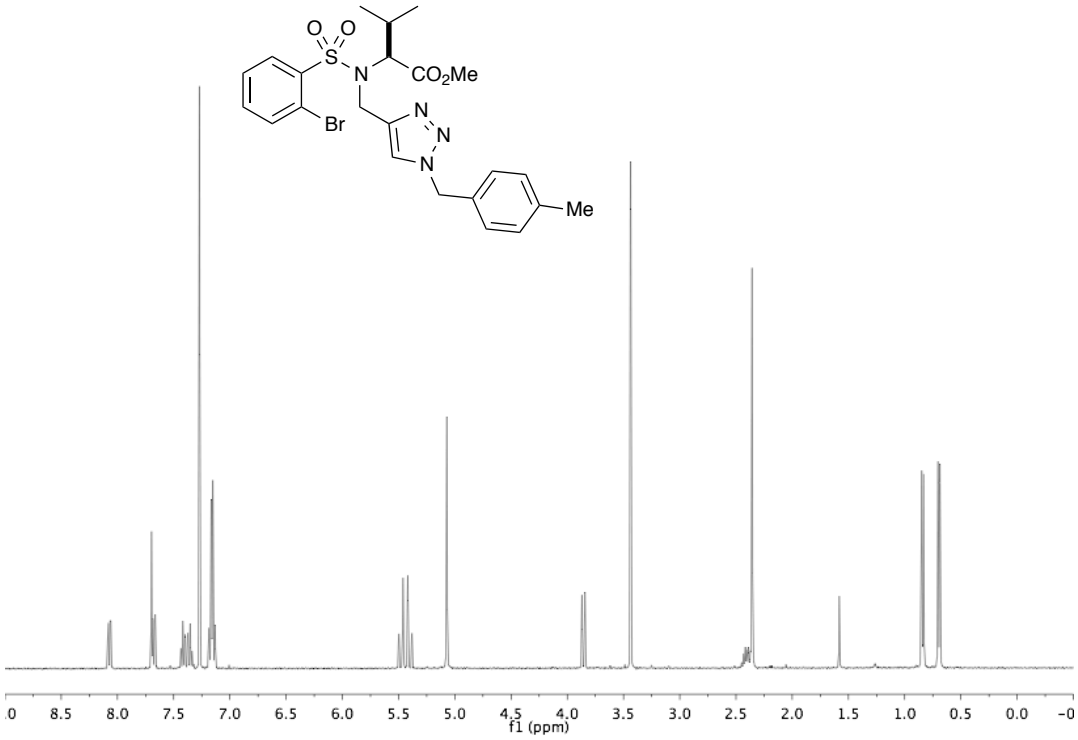


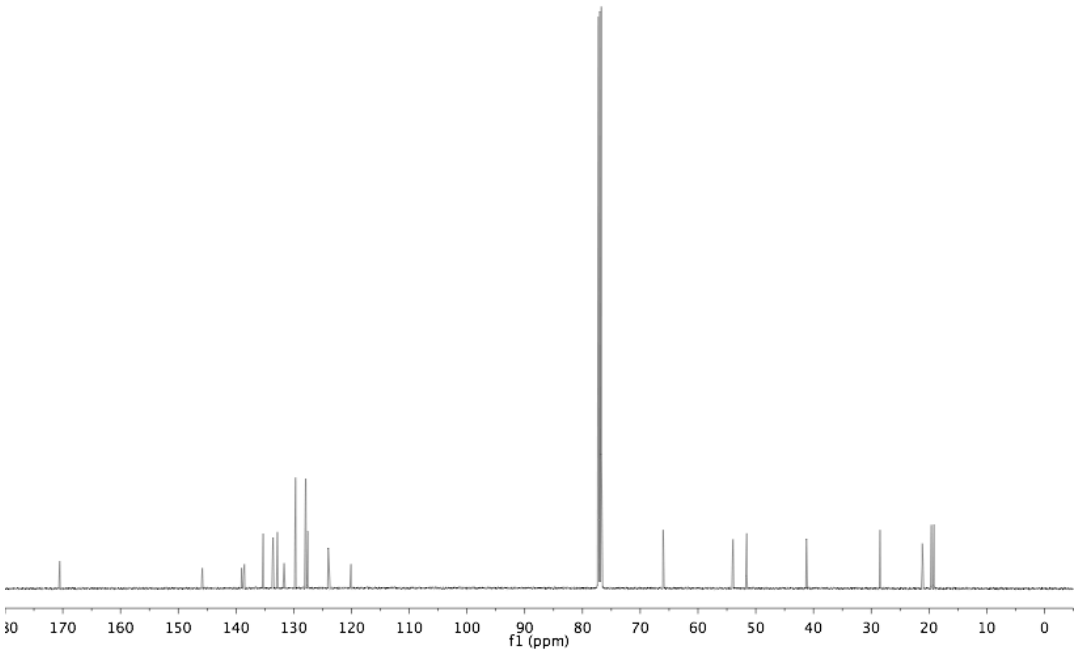
(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.28)



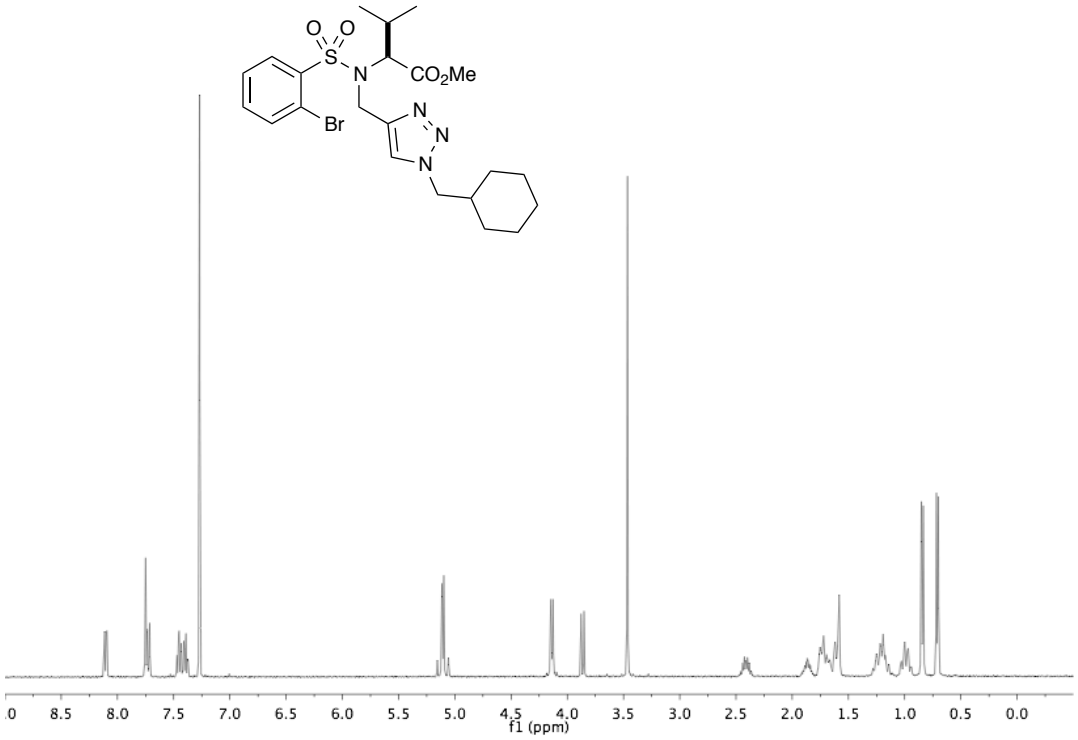


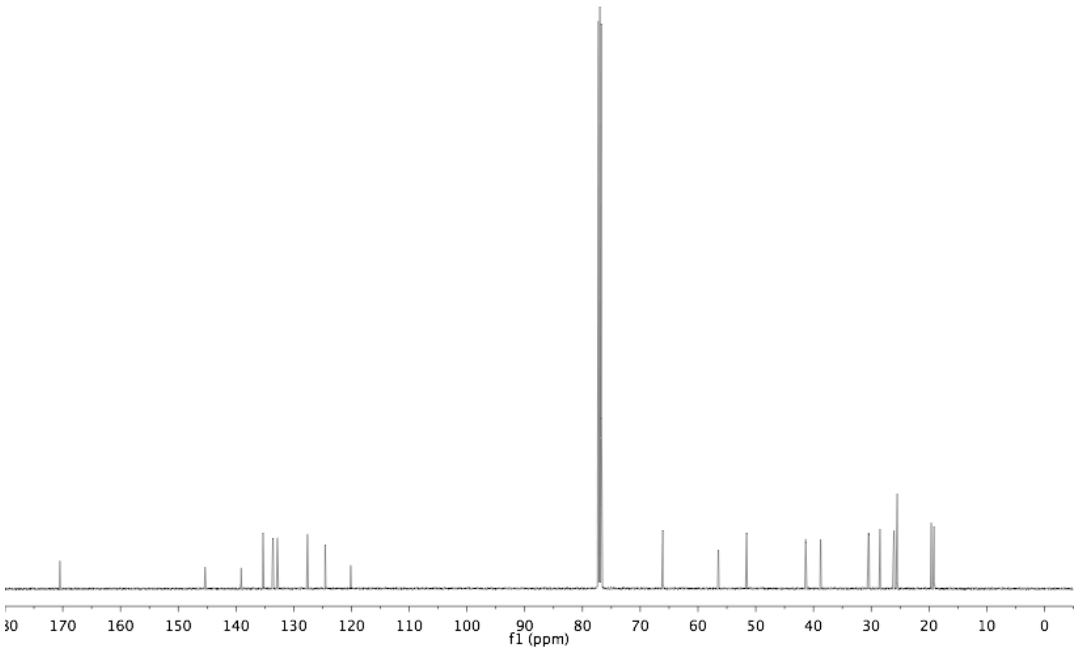
(*S*)-Methyl 2-(2-bromo-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.29)



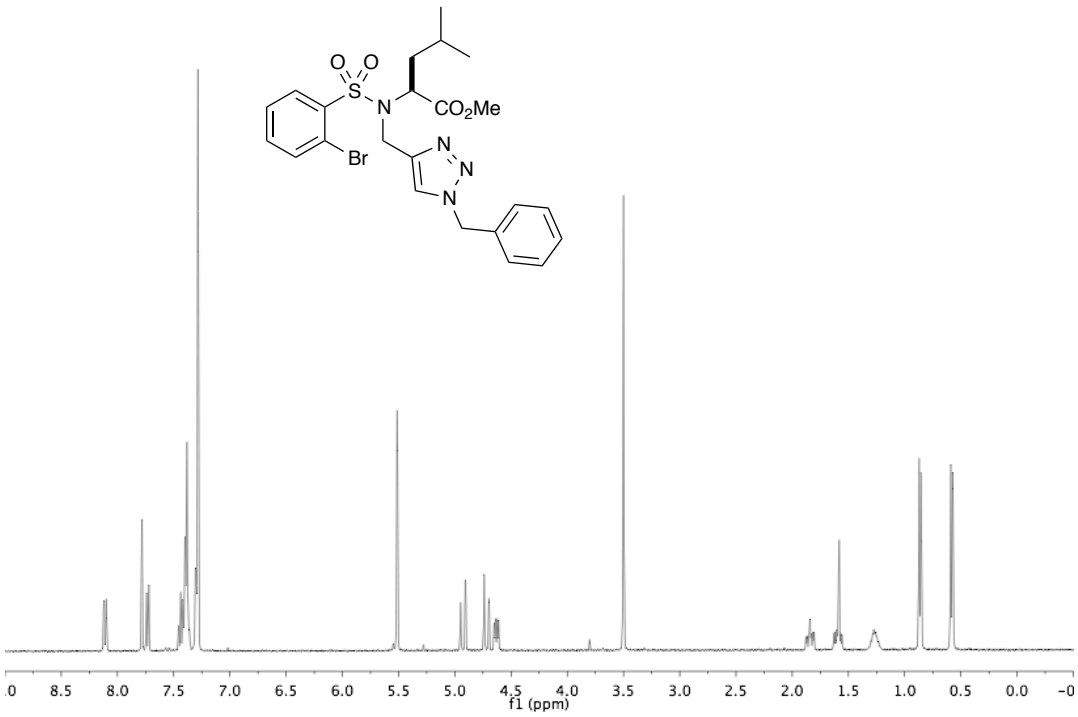


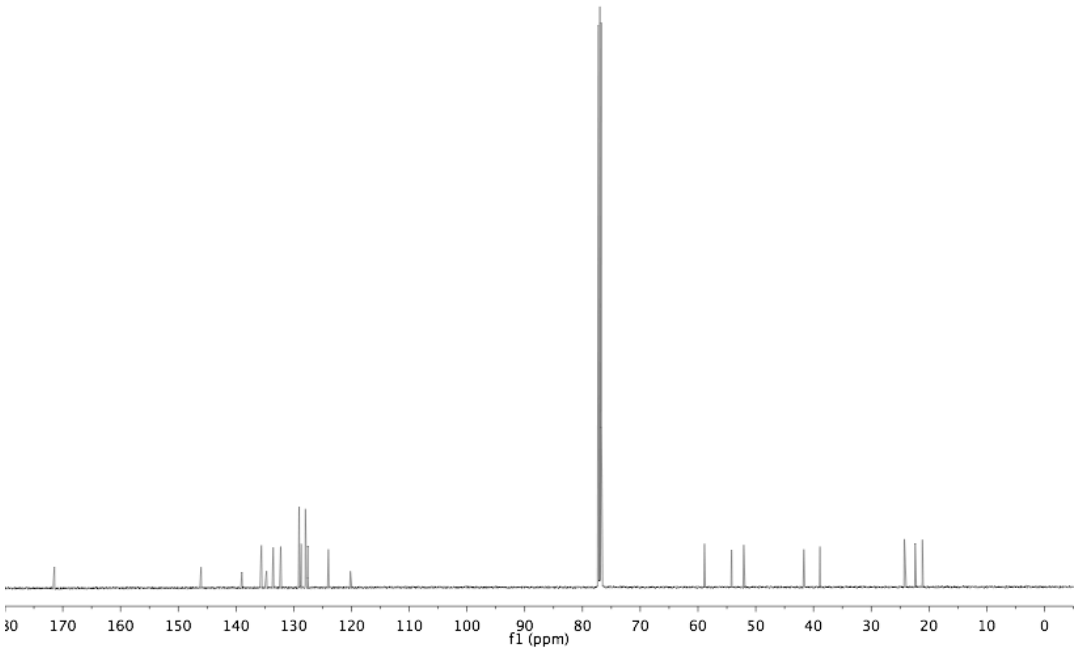
(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.30)



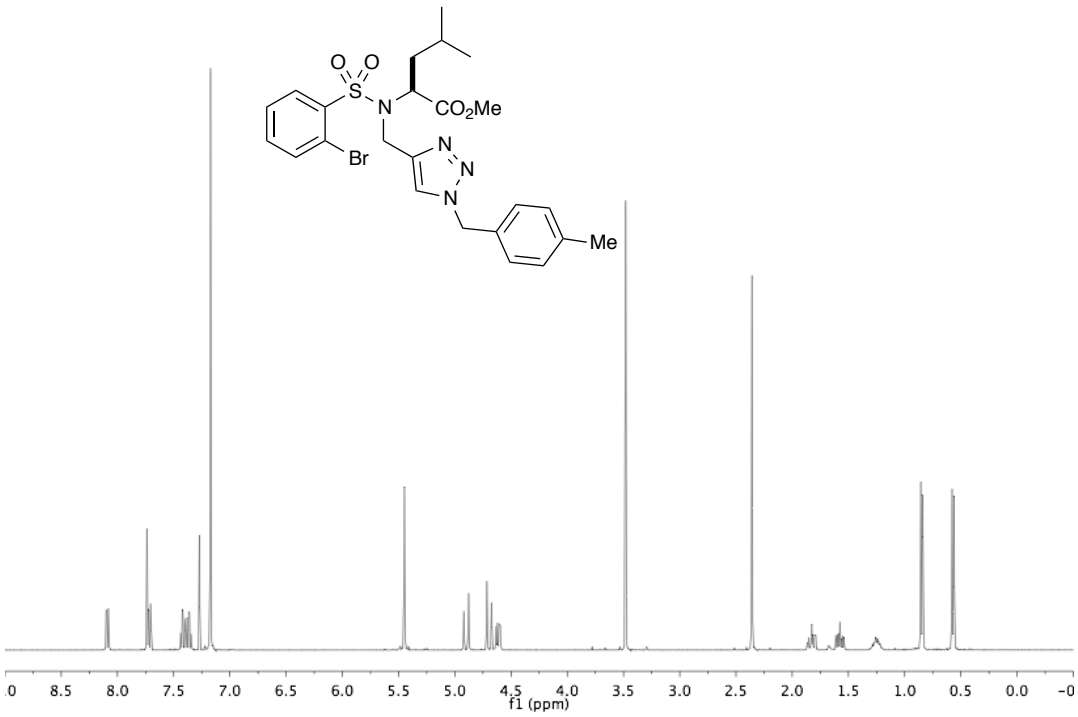


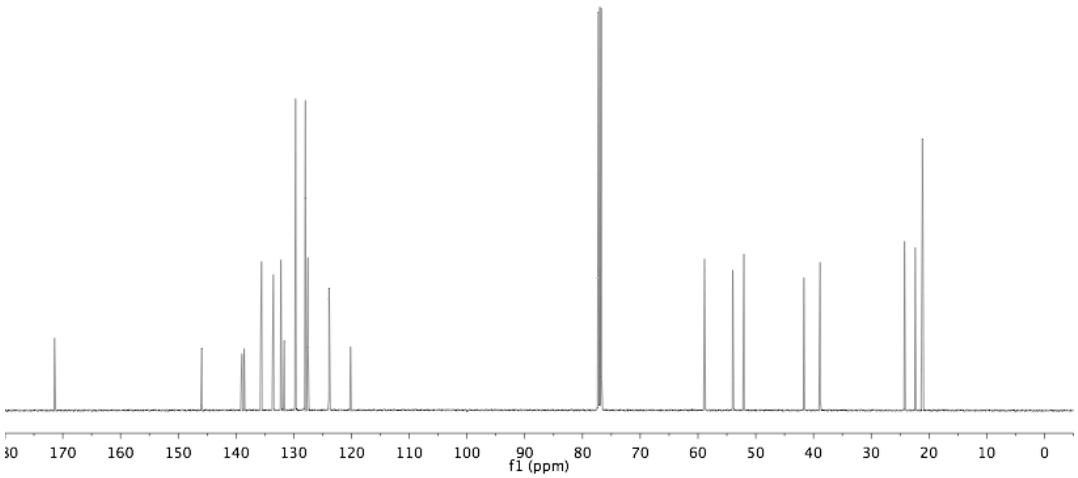
(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromophenylsulfonamido)-4-methylpentanoate (4.31)



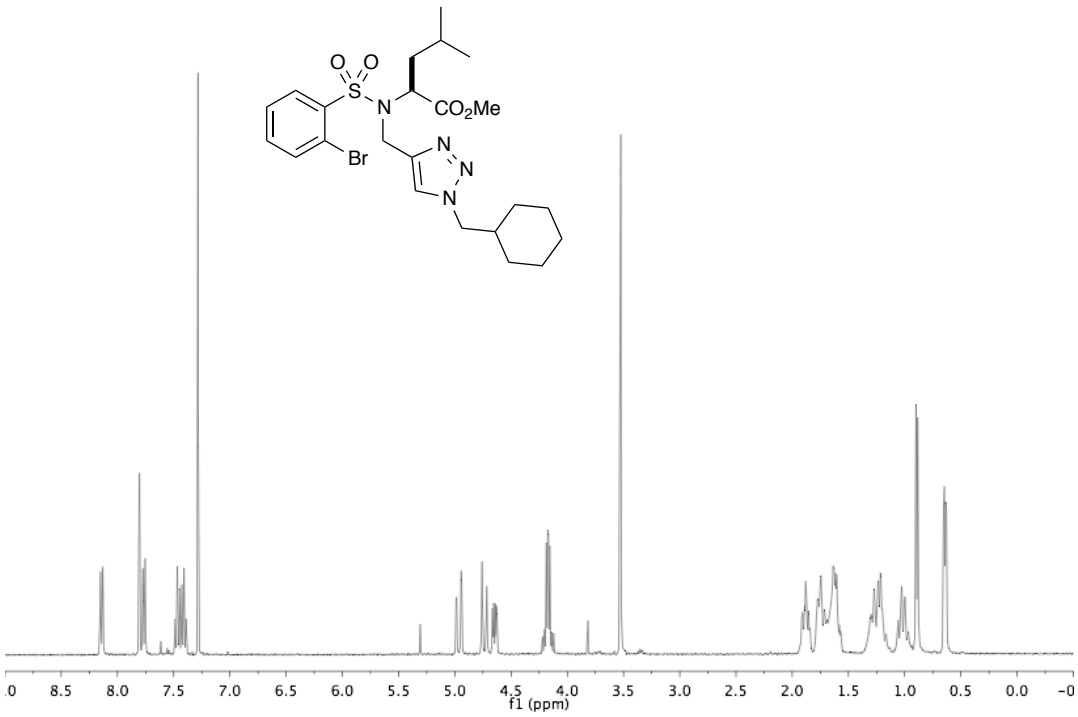


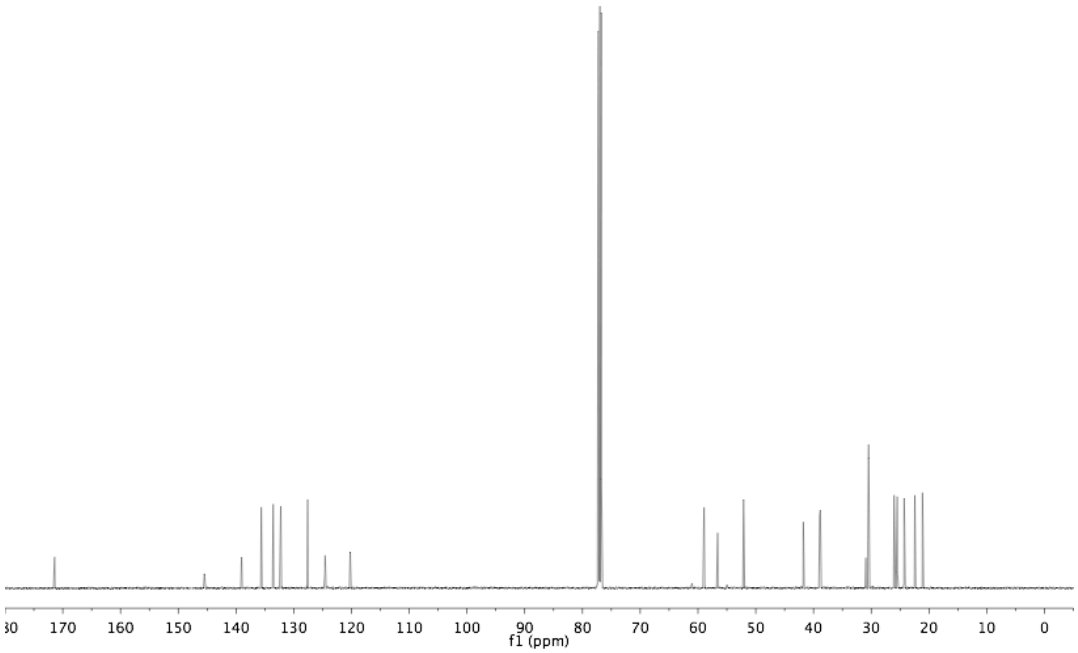
(*S*)-Methyl 2-(2-bromo-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.32)



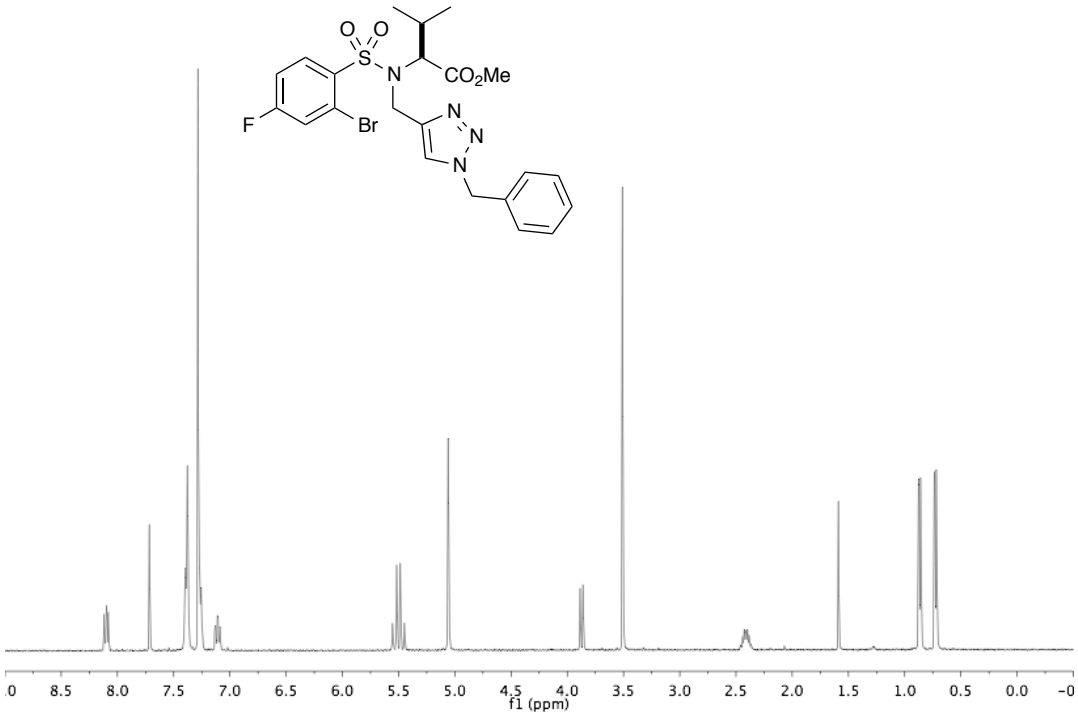


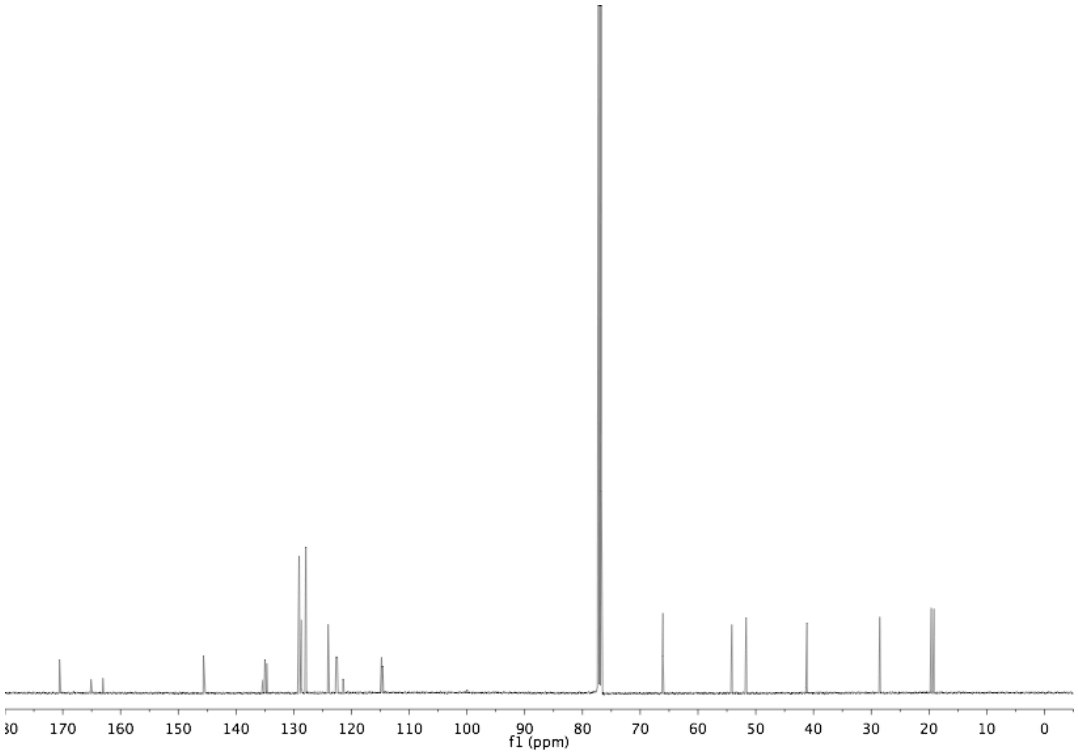
(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.33)



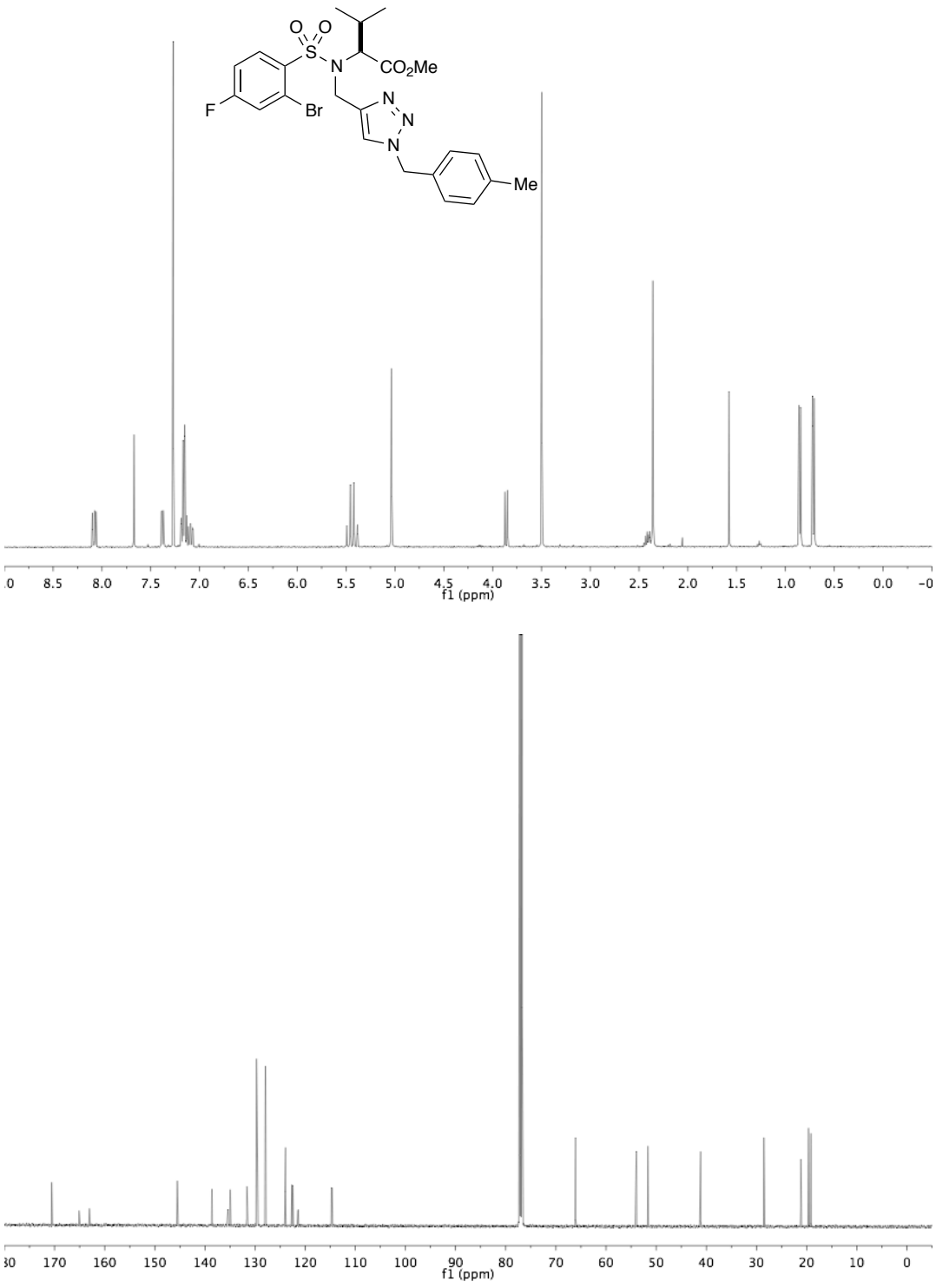


(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-4-fluorophenylsulfonamido)-3-methylbutanoate (4.34)

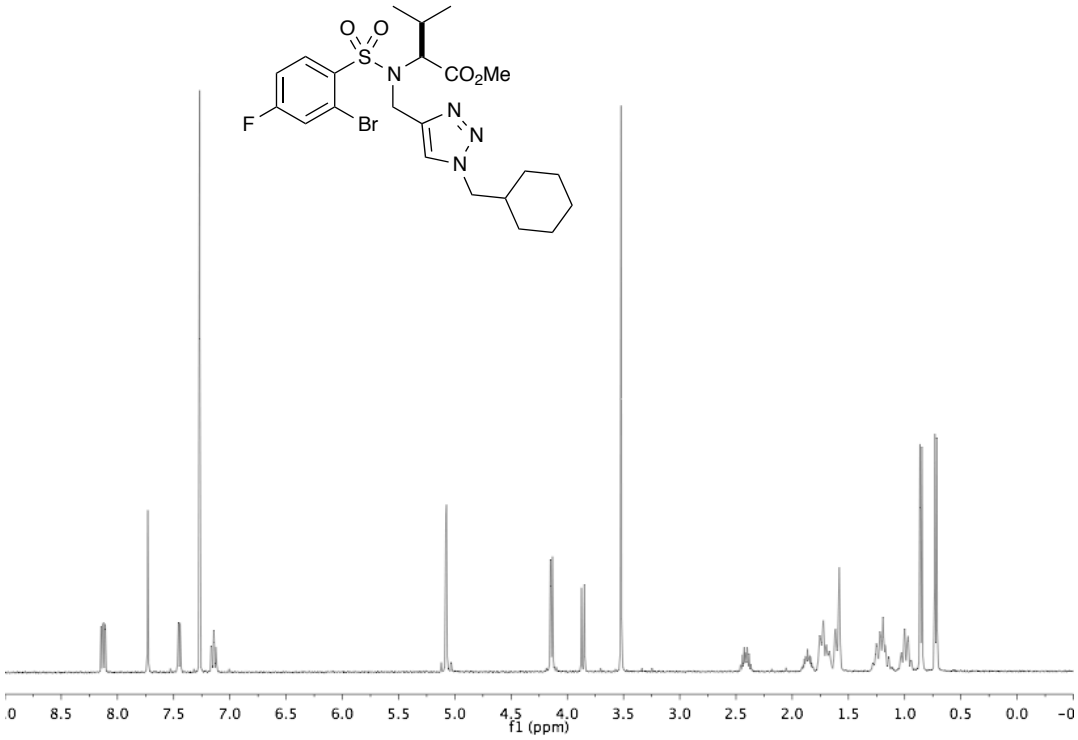


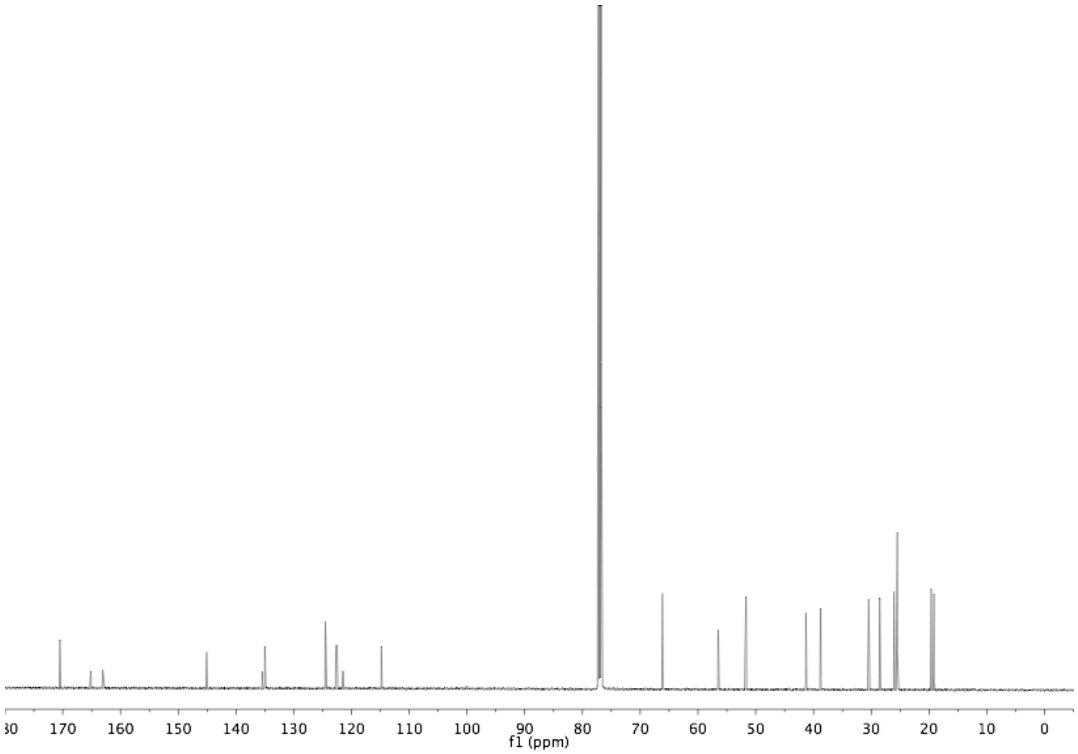


(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.35)

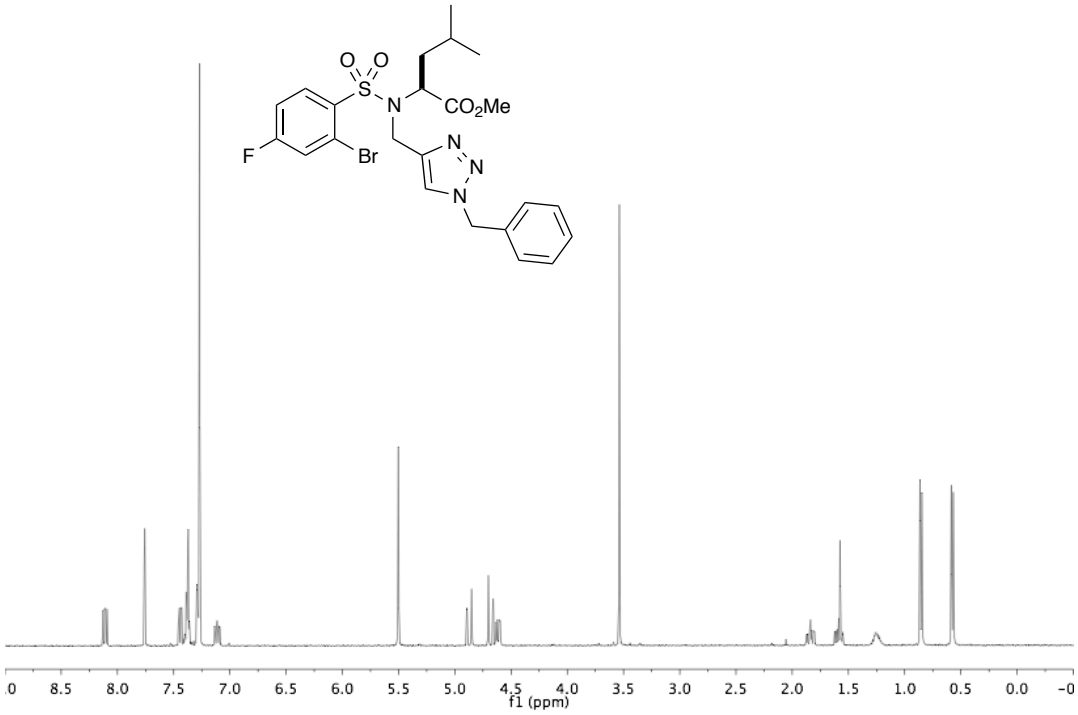


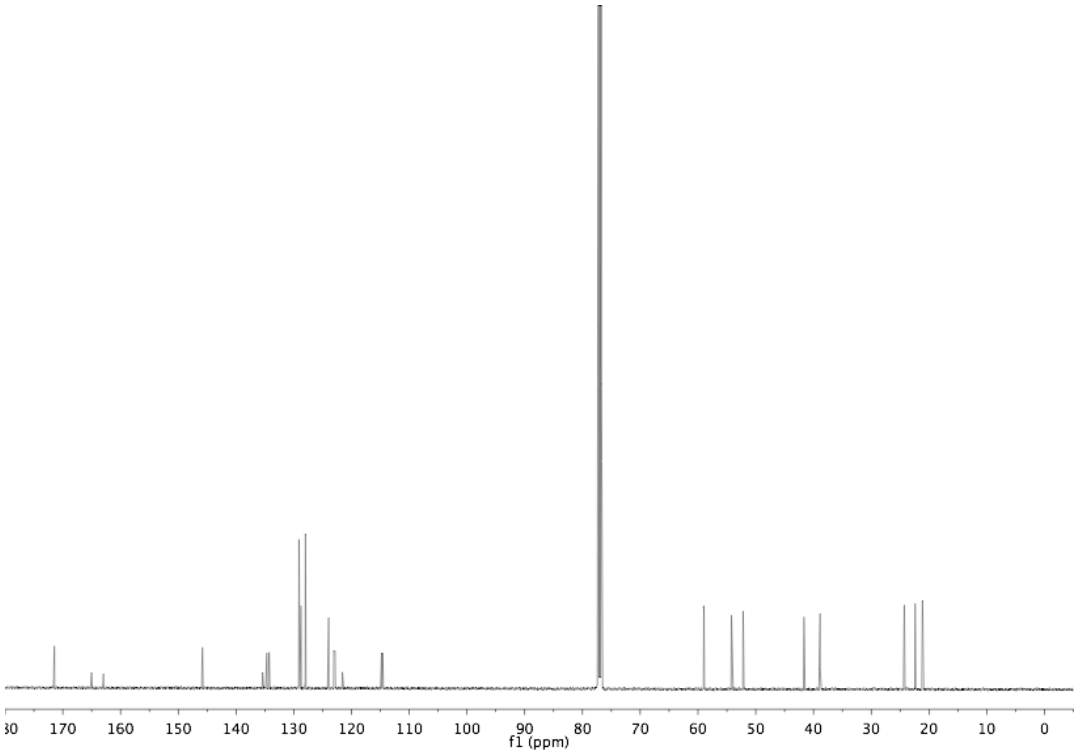
(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.36)



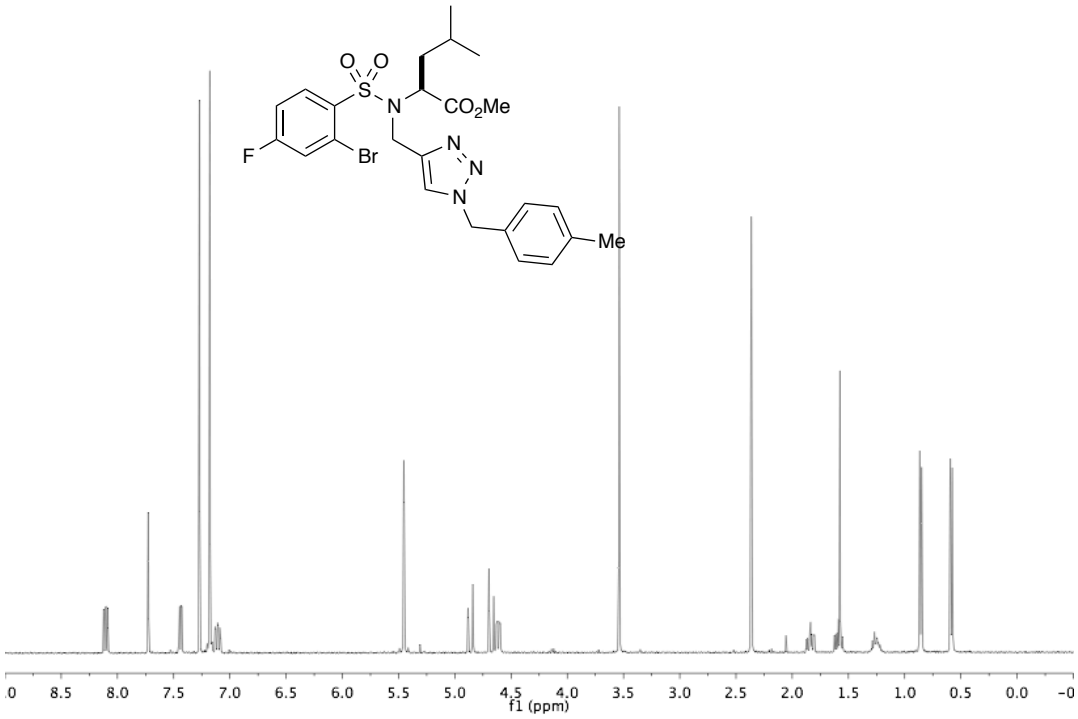


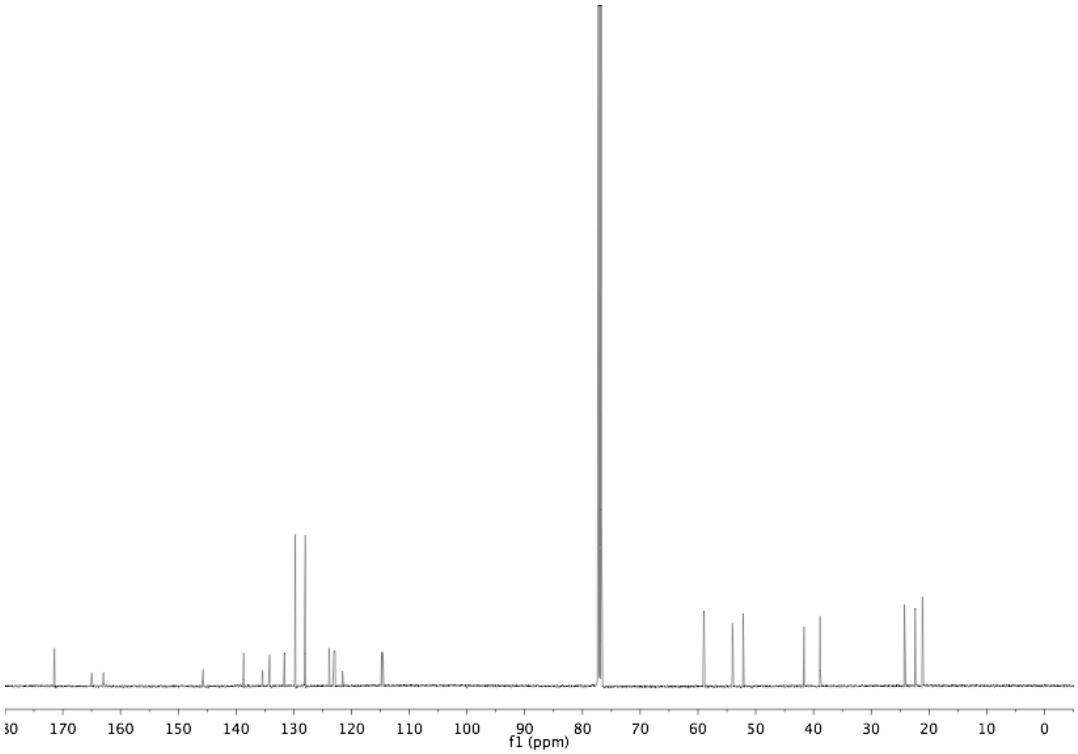
(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-4-fluorophenylsulfonamido)-4-methylpentanoate (4.37)



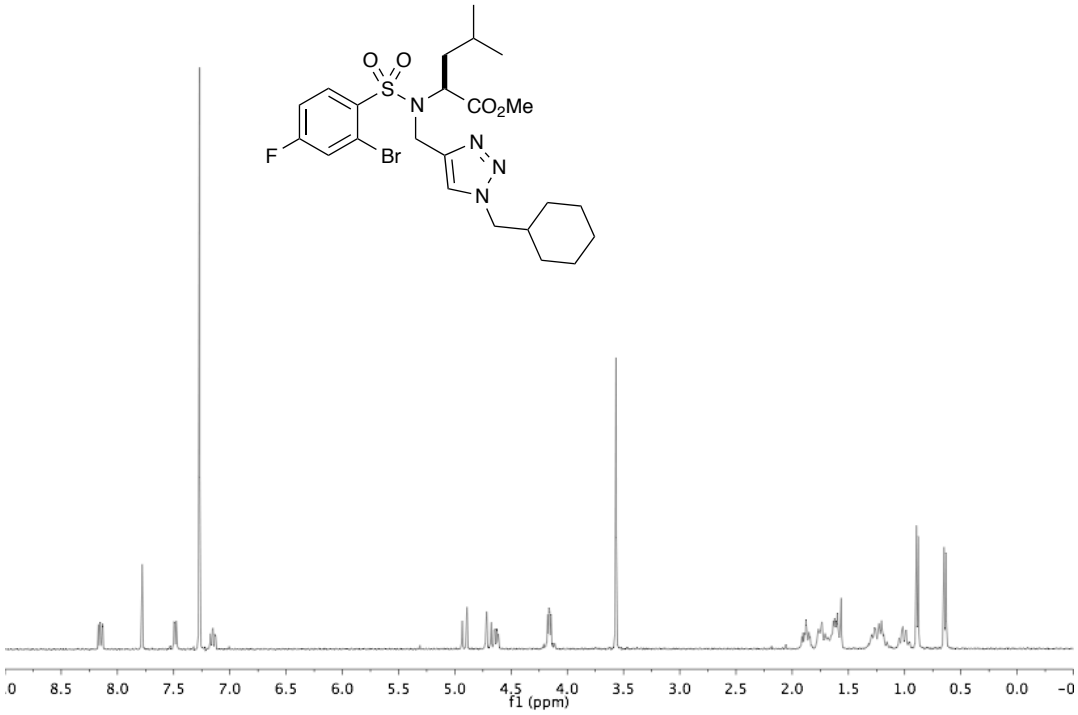


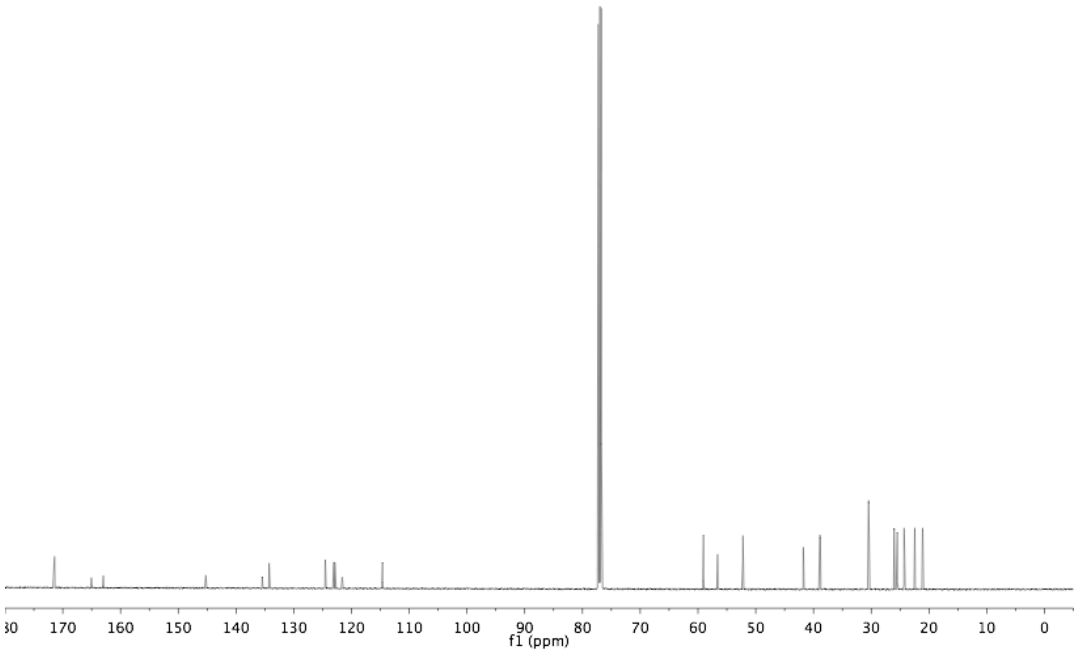
(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.38)



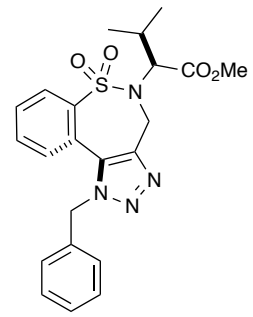


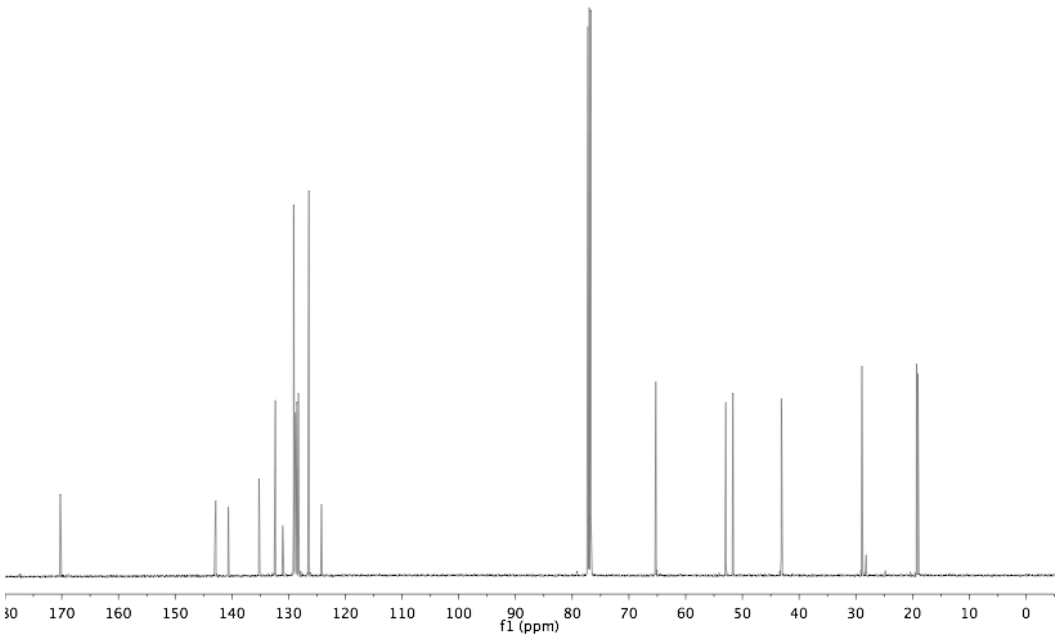
(*S*)-Methyl 2-(2-bromo-*N*-((1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-fluorophenylsulfonamido)-4-methylpentanoate (4.39)



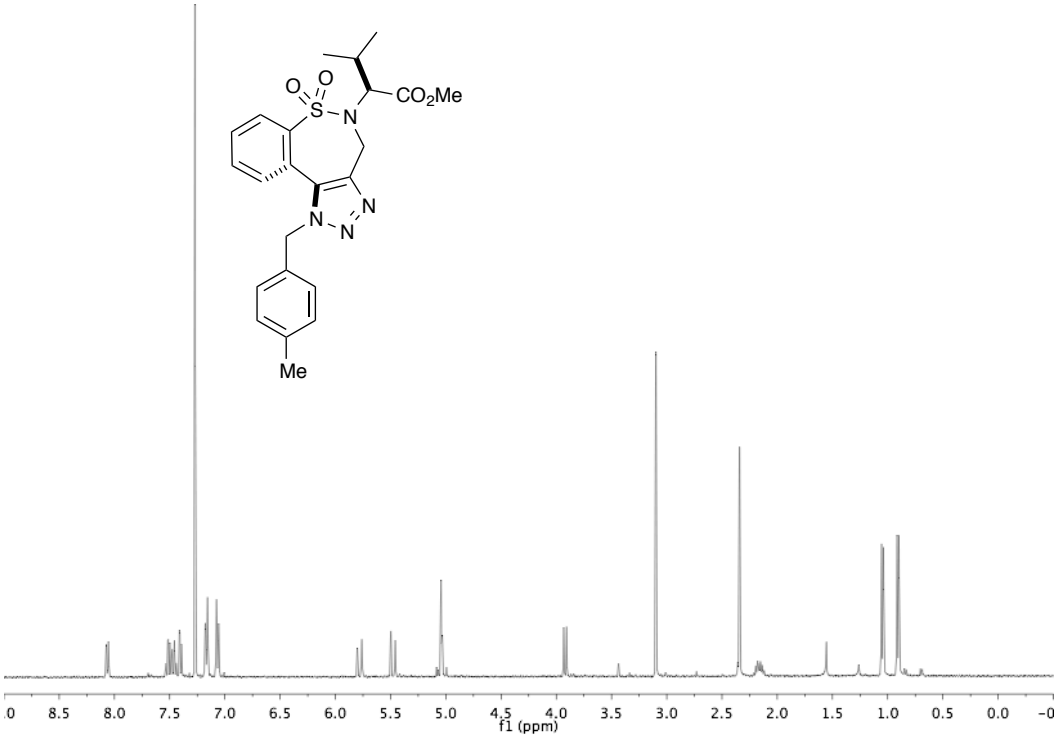


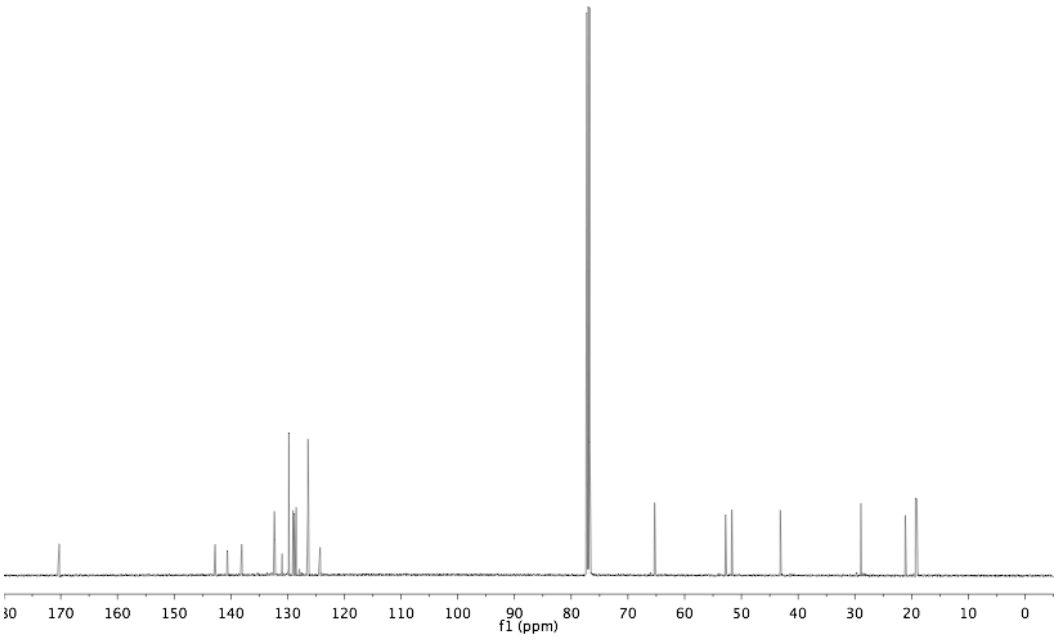
(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.40)



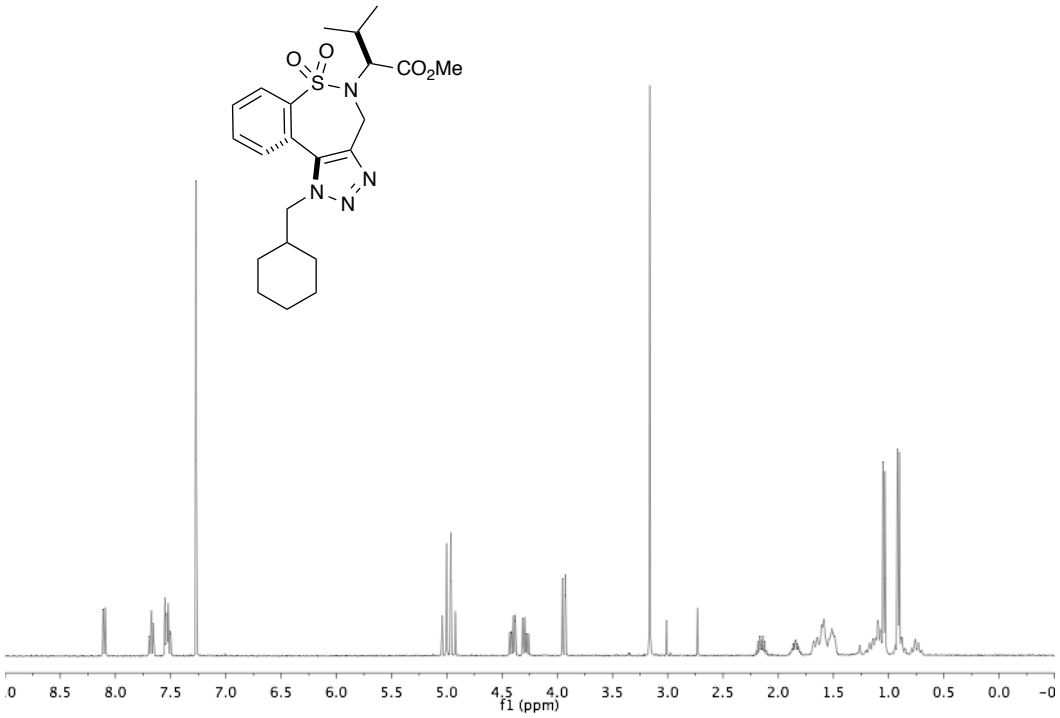


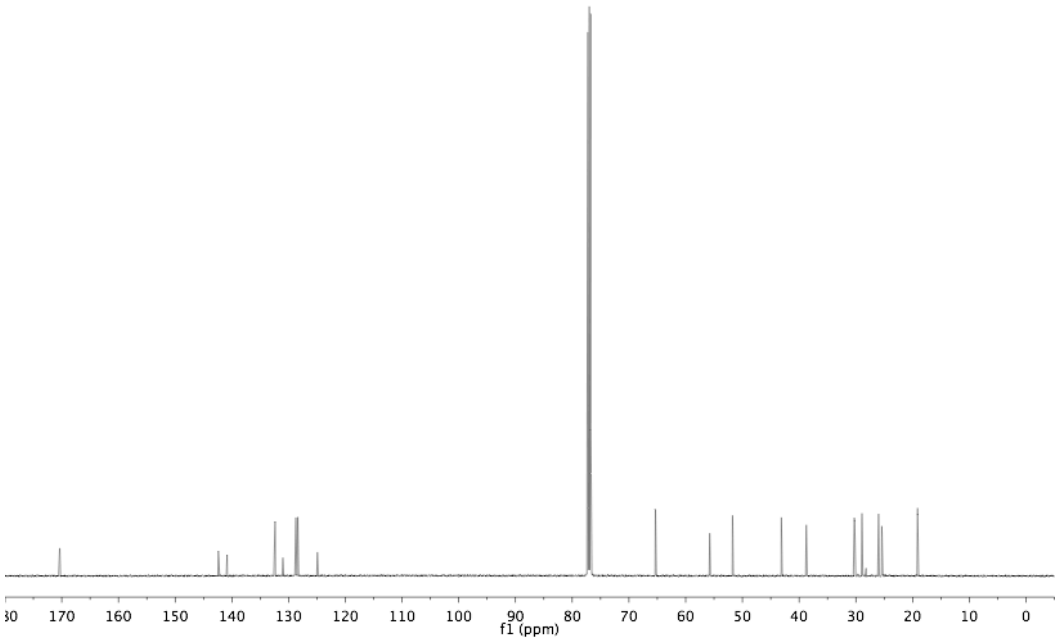
(*S*)-Methyl 3-methyl-2-((*S*$_a$)-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)butanoate (4.41)



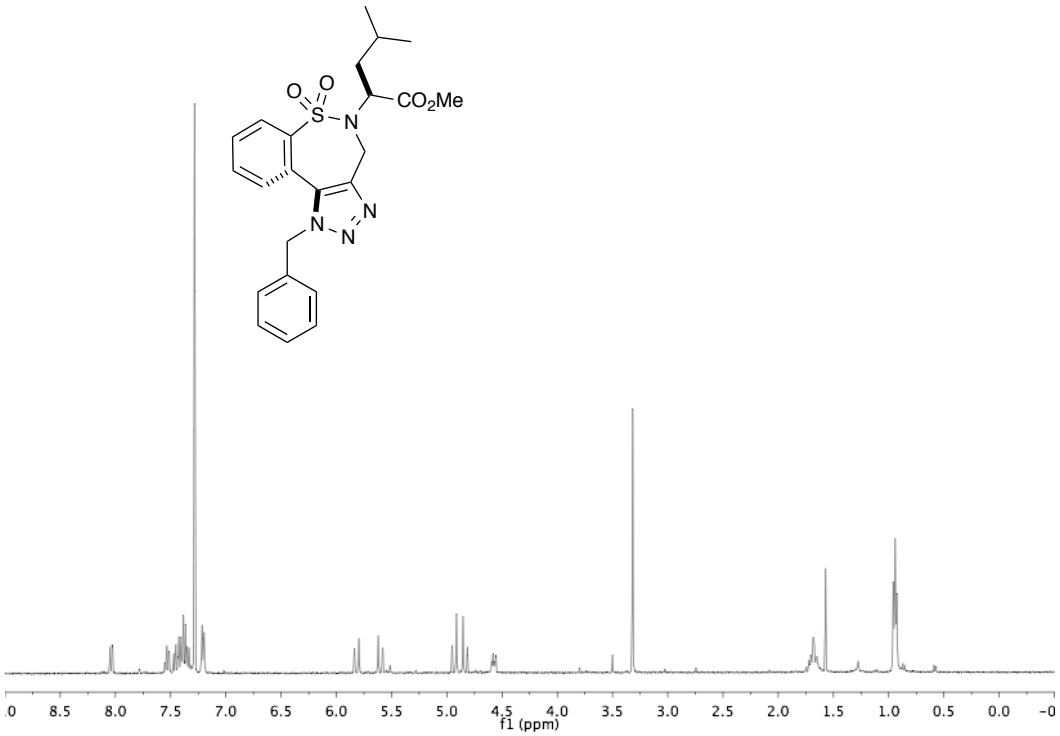


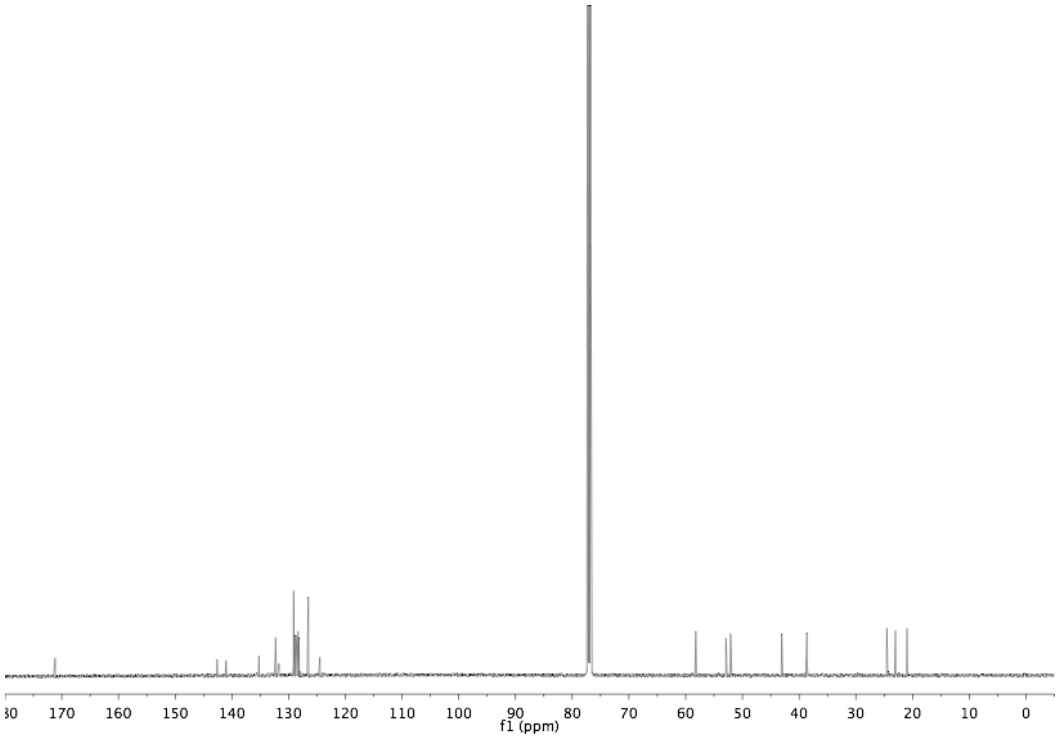
(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.42)



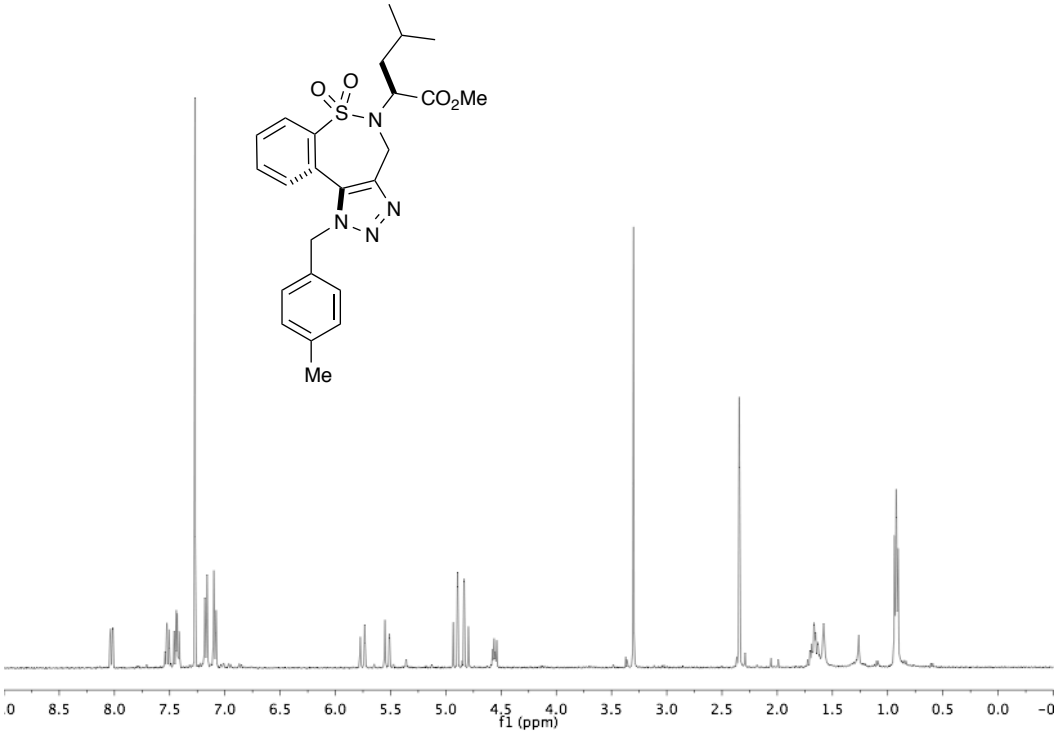


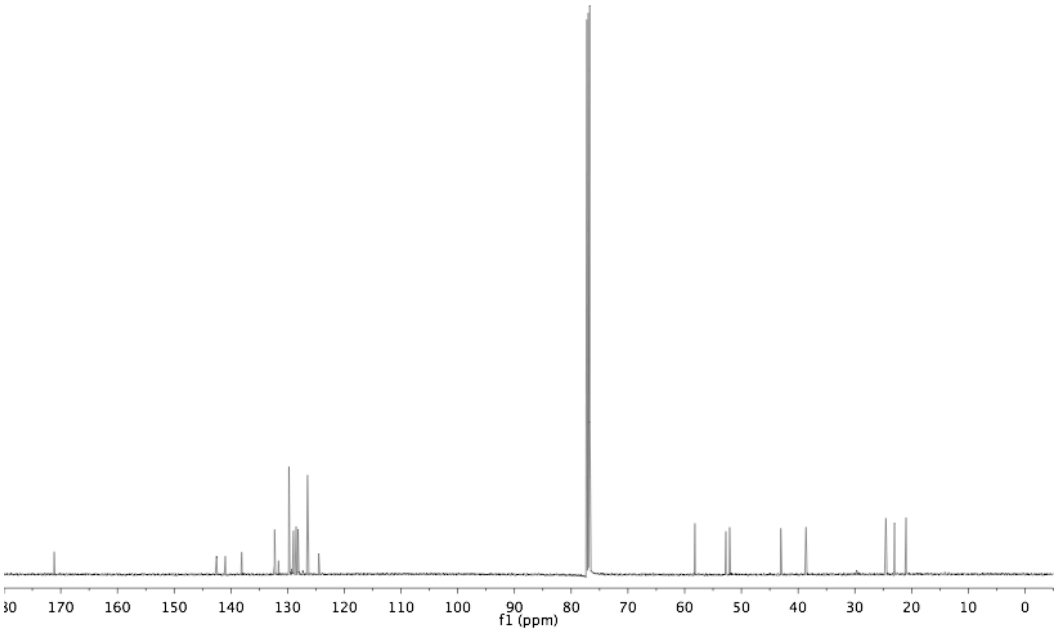
(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.43)



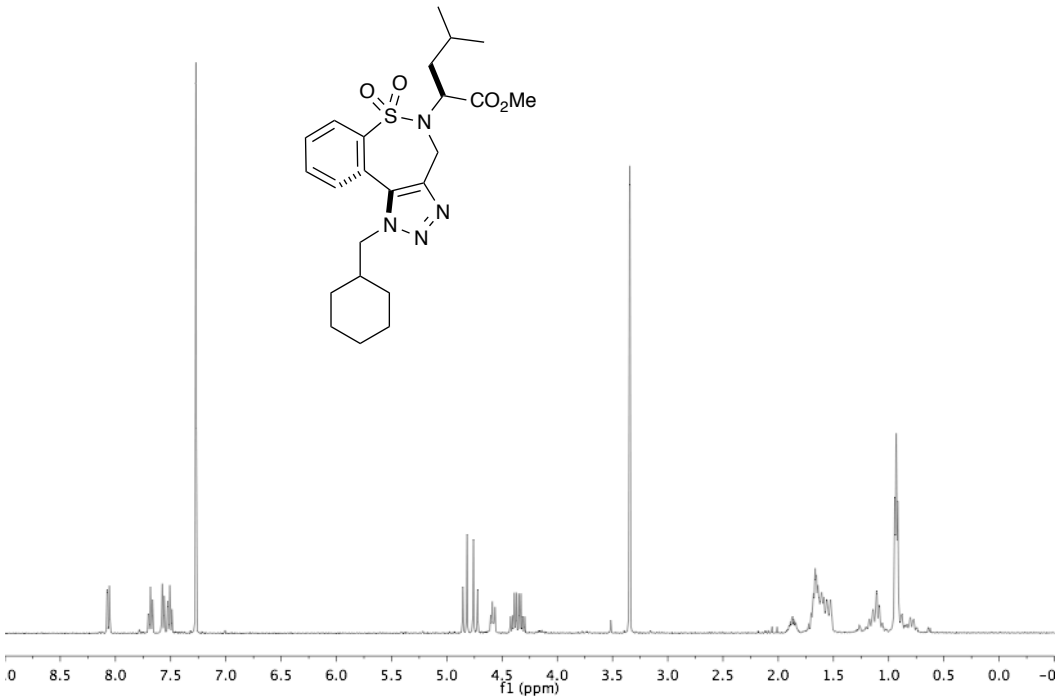


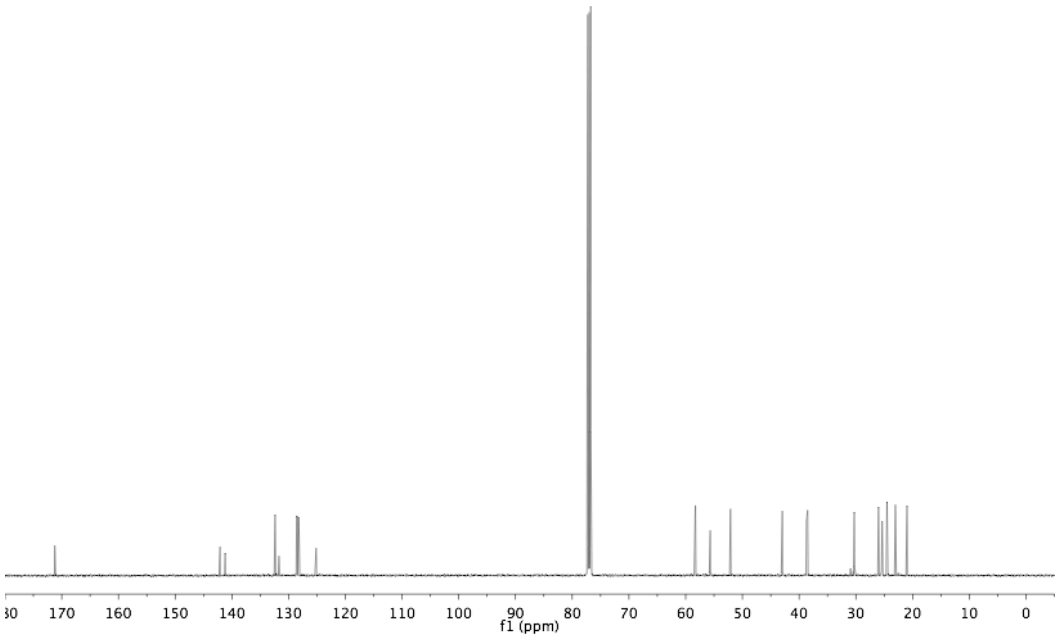
(*S*)-Methyl 4-methyl-2-((*S*$_a$)-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)pentanoate (4.44)



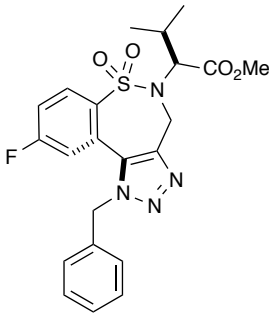


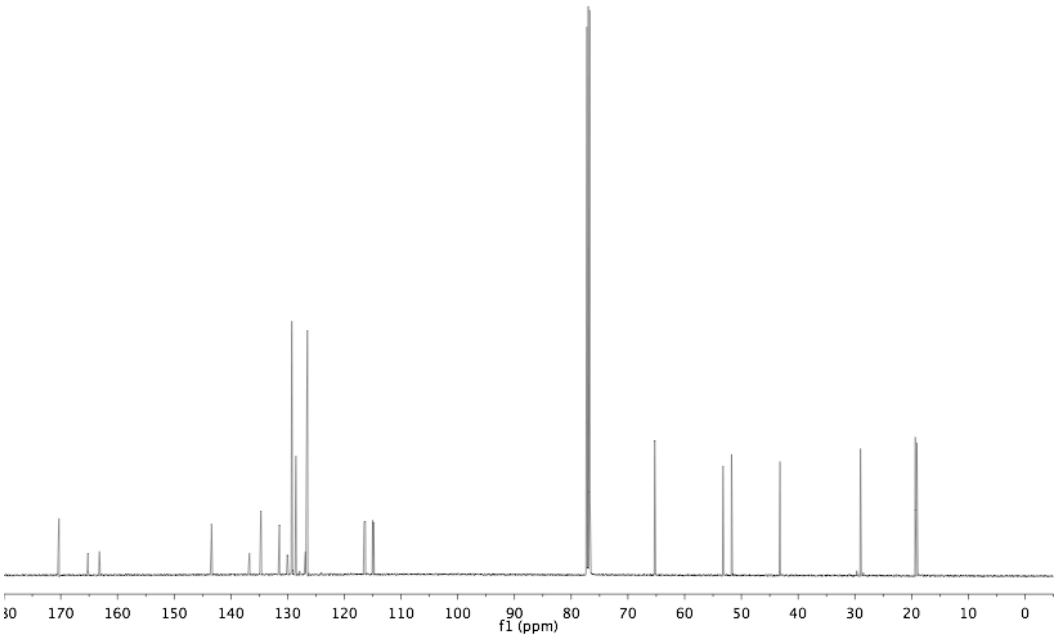
(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.45)



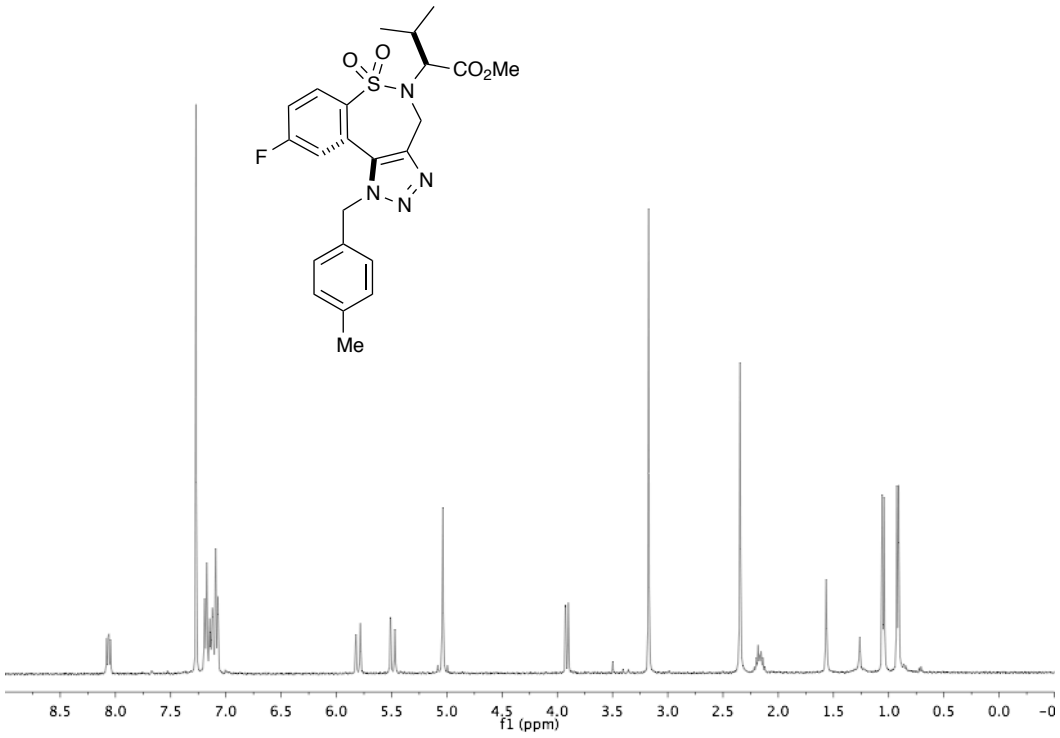


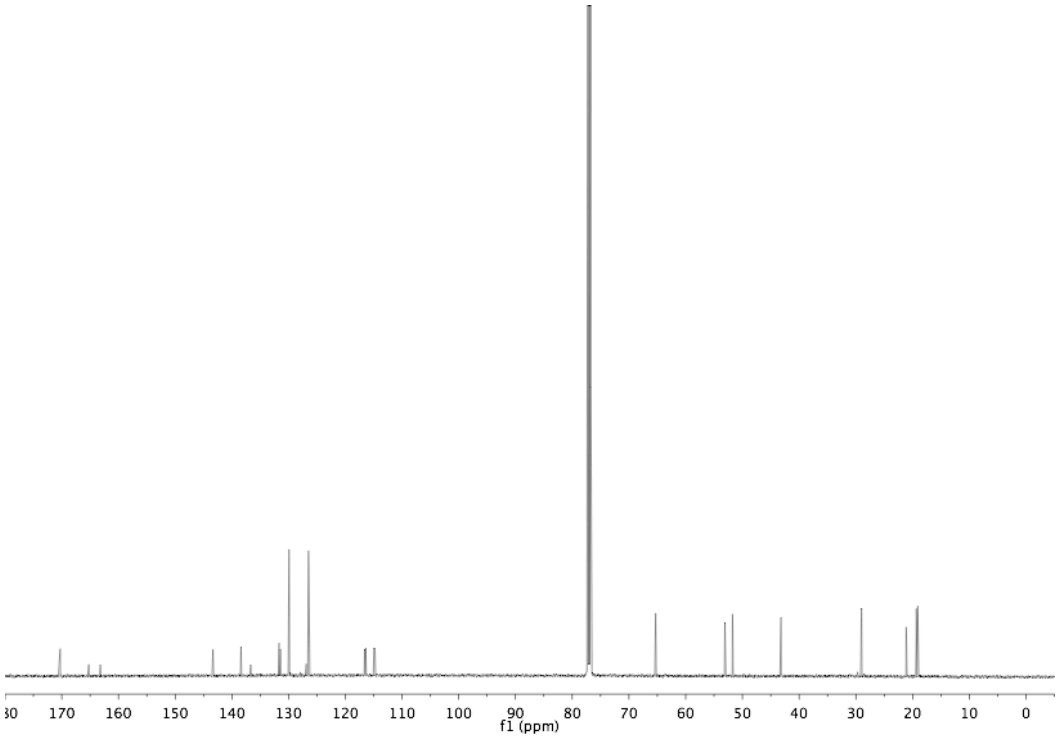
(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.46)



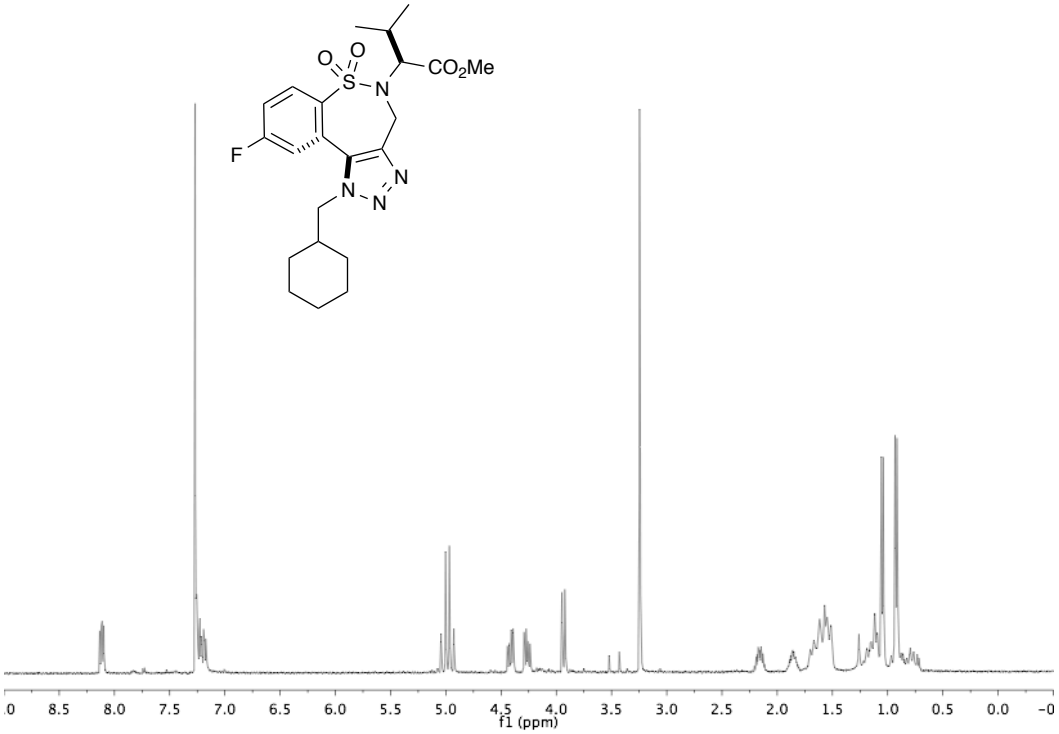


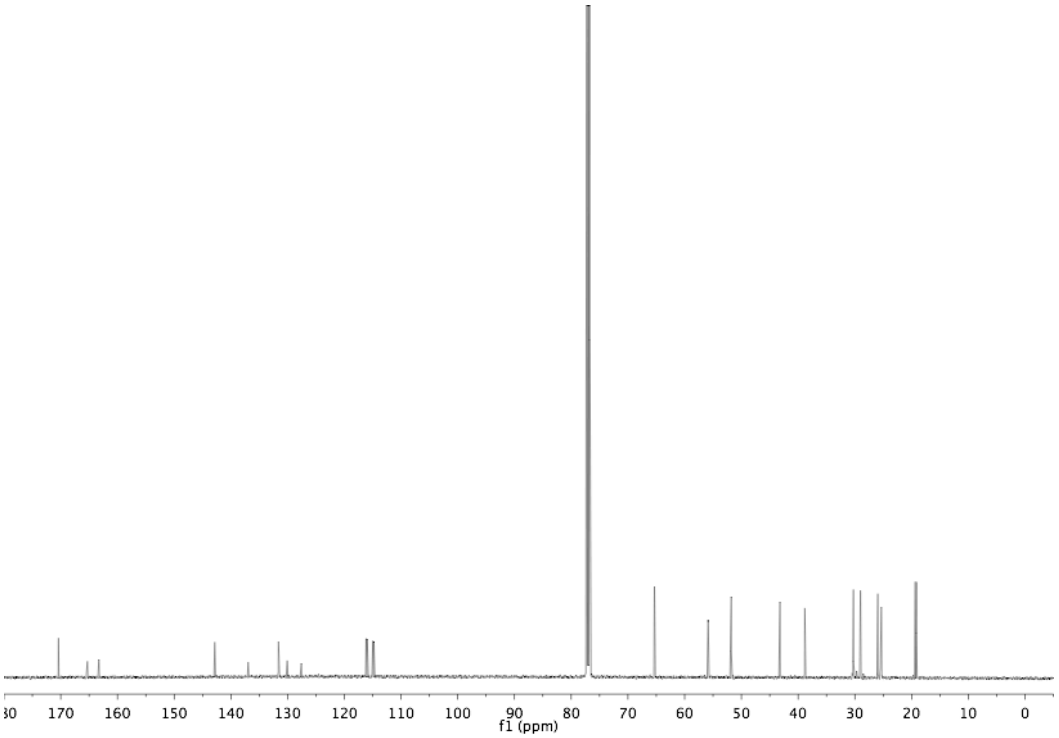
(*S*)-Methyl 2-((*S*$_a$)-9-fluoro-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.47)



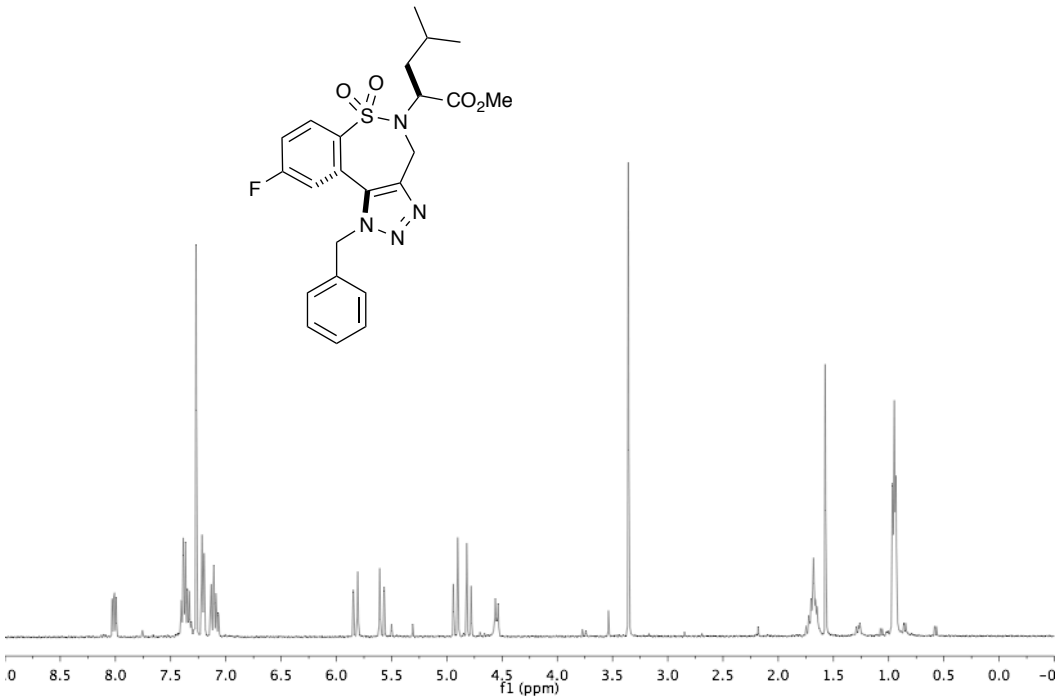


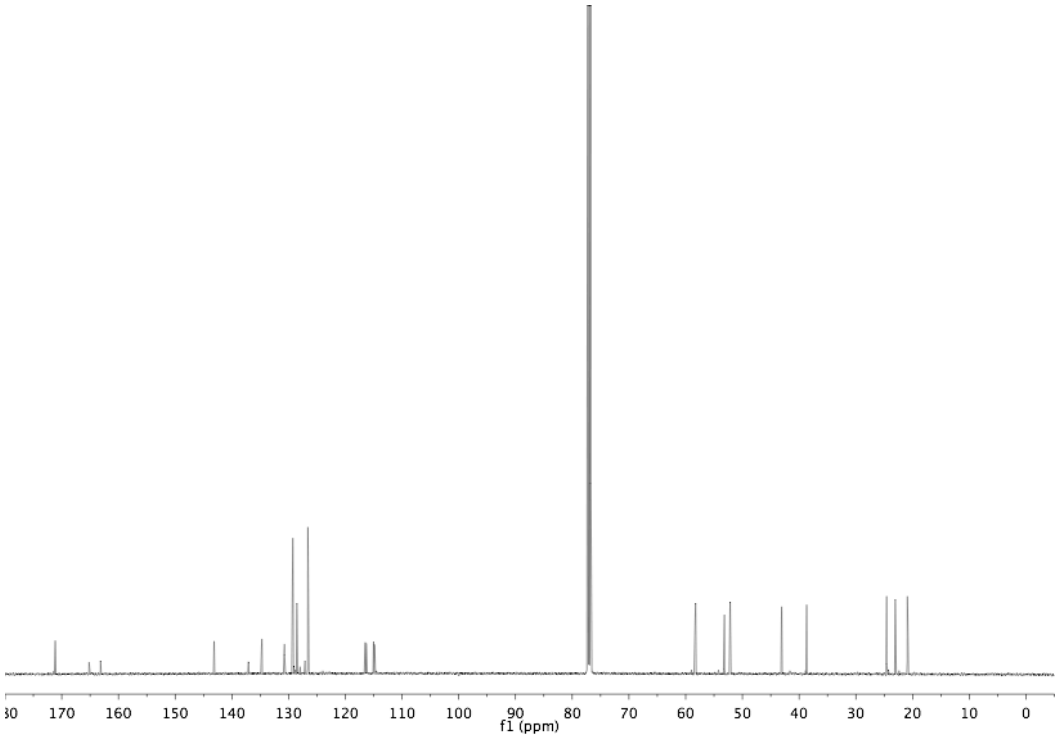
(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.48)



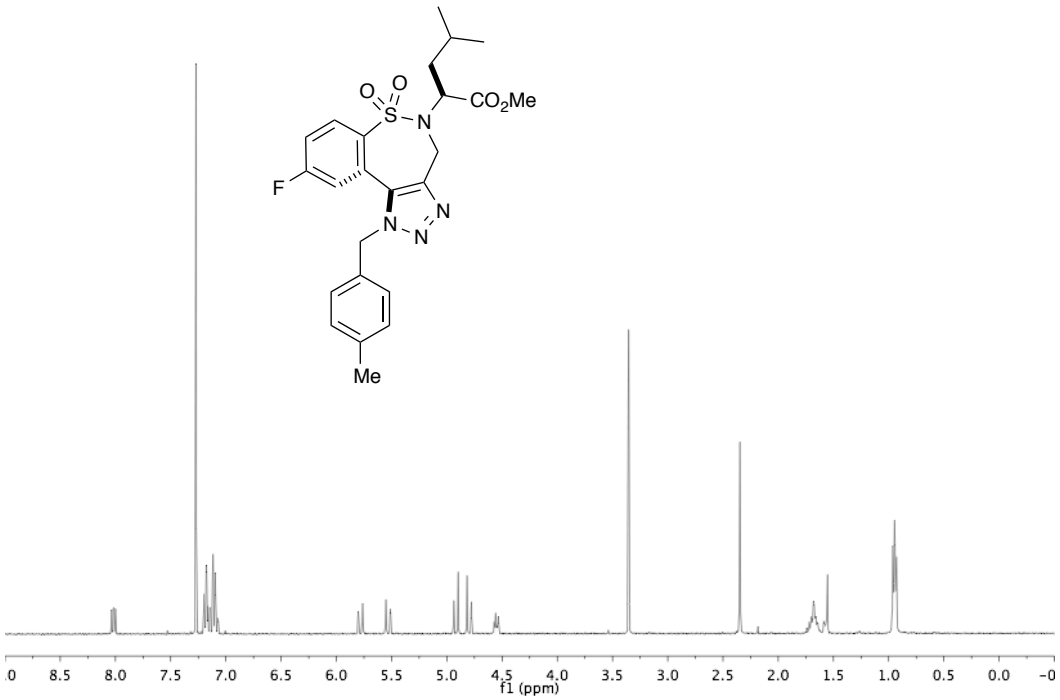


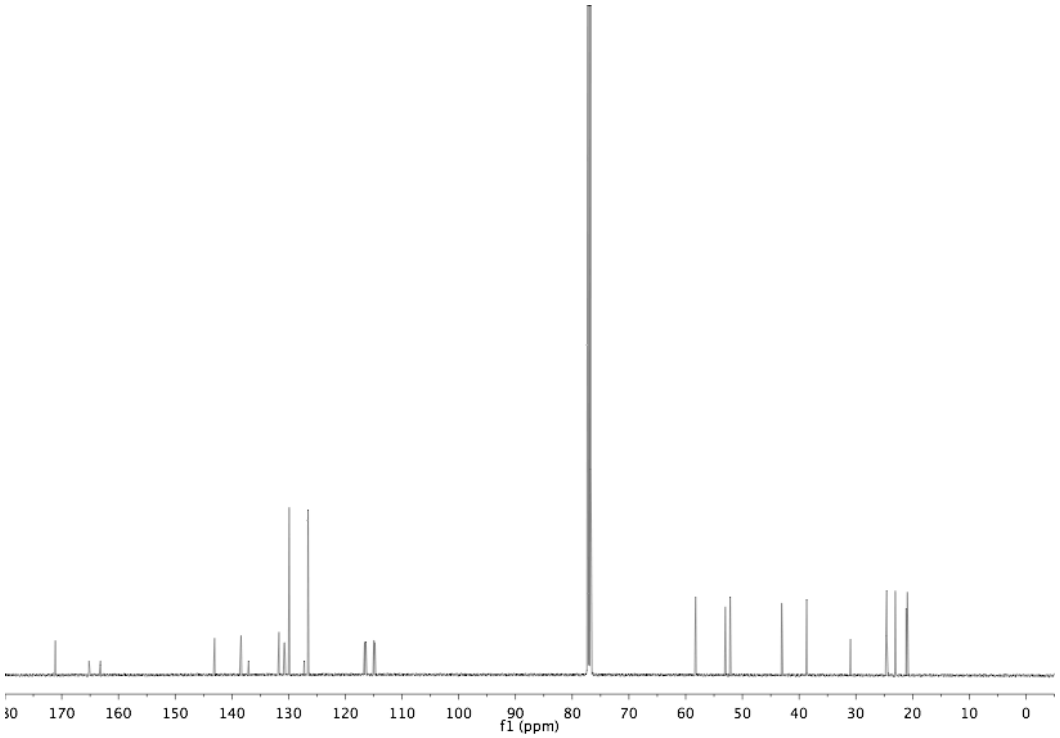
(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.49)



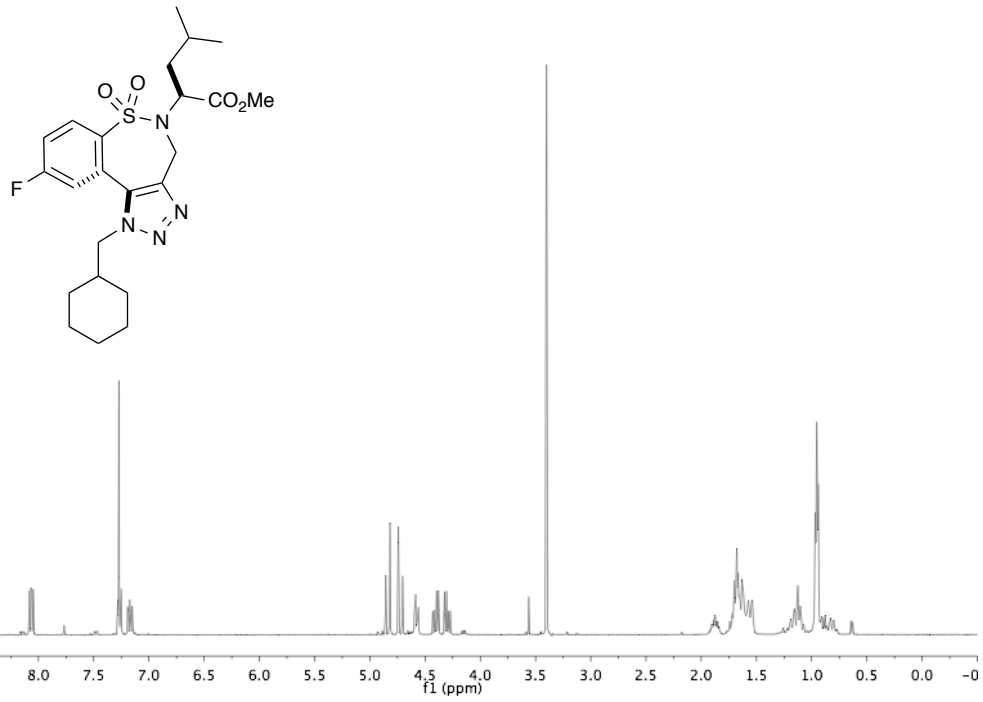


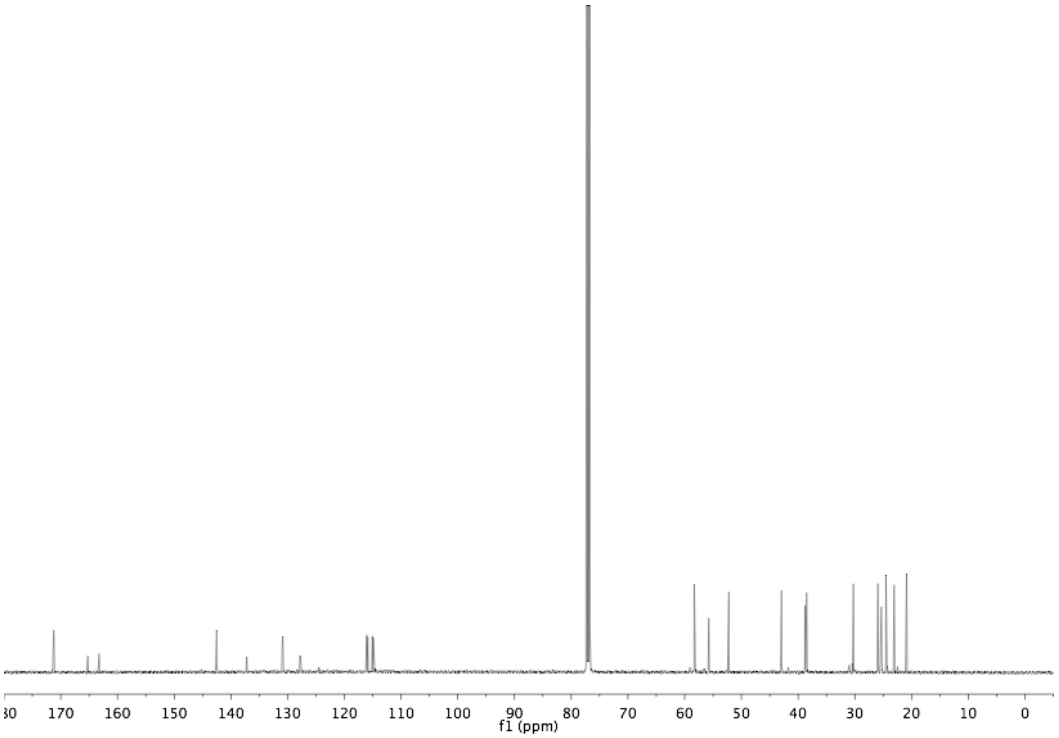
(*S*)-Methyl 2-((*S*$_a$)-9-fluoro-1-(4-methylbenzyl)-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.50)



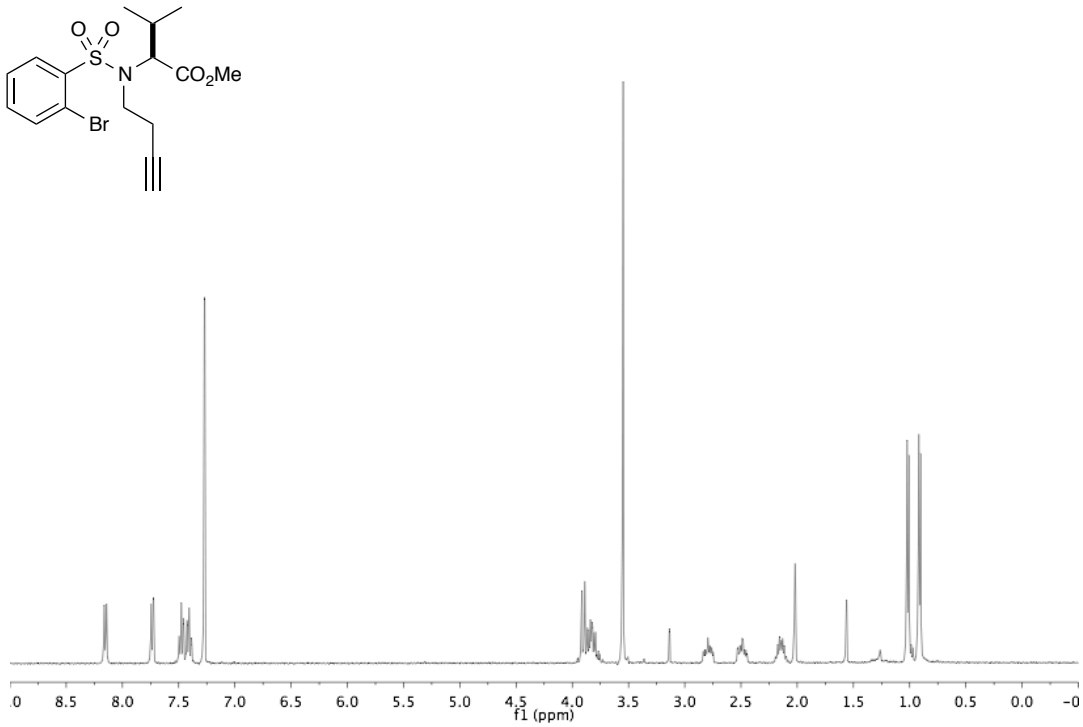


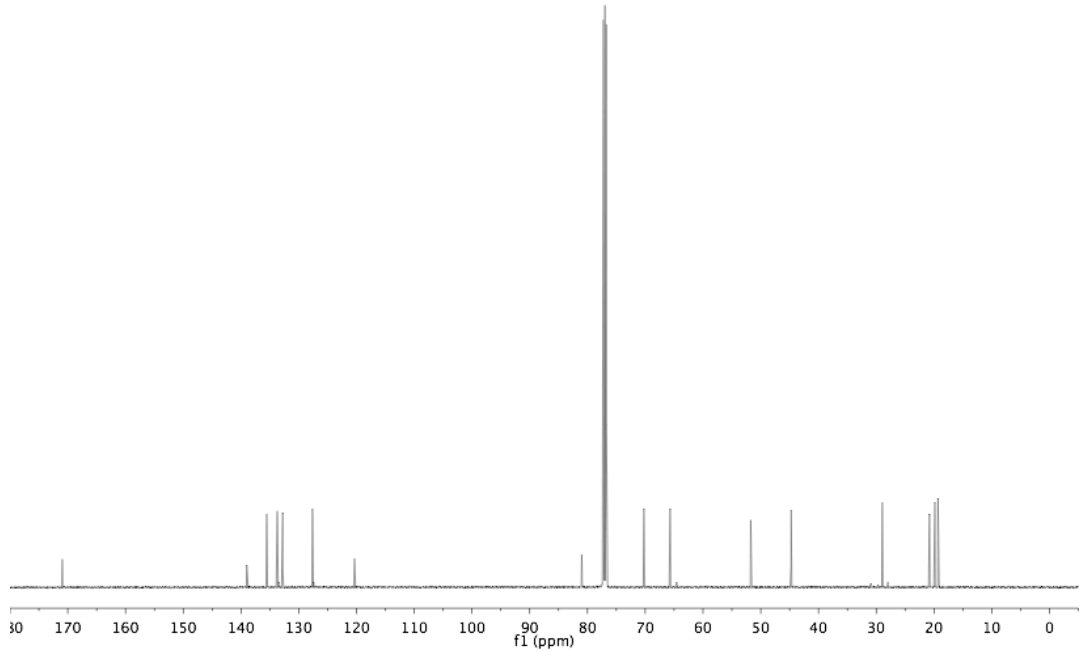
(*S*)-Methyl 2-((*S*$_a$)-1-(cyclohexylmethyl)-9-fluoro-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.51)



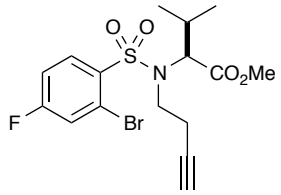


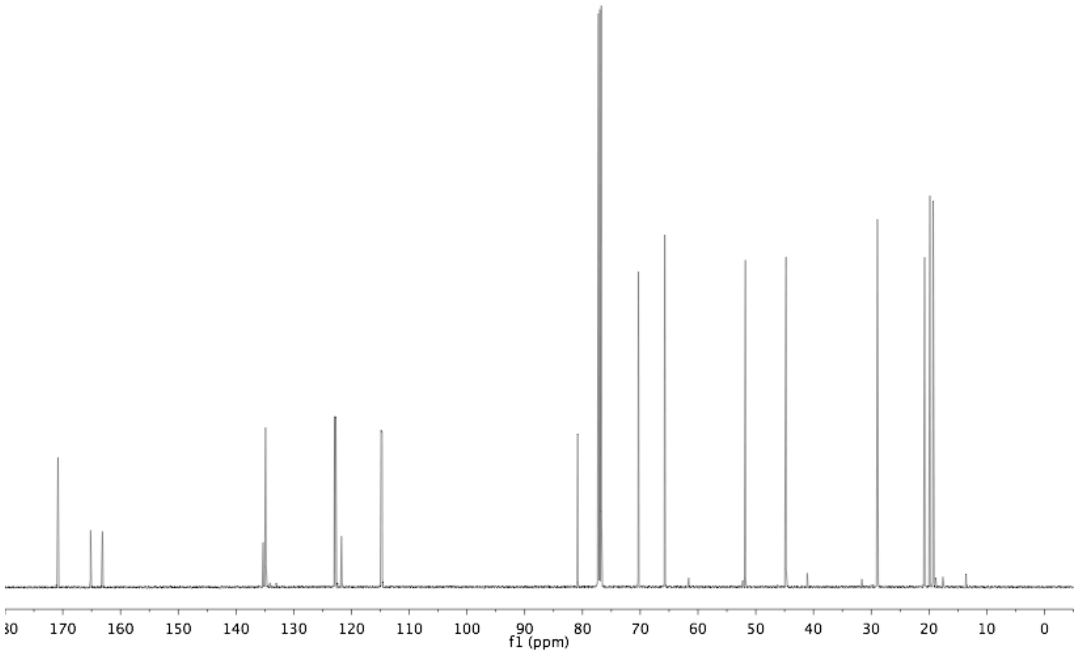
(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)phenylsulfonamido)-3-methylbutanoate (4.52)



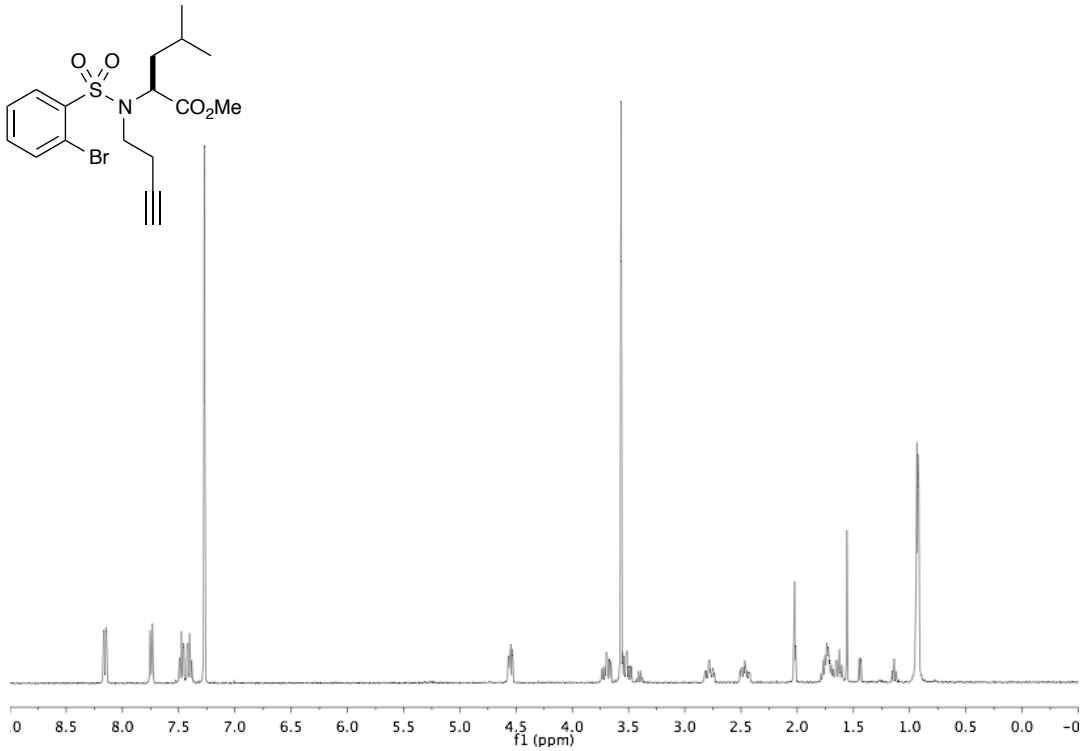


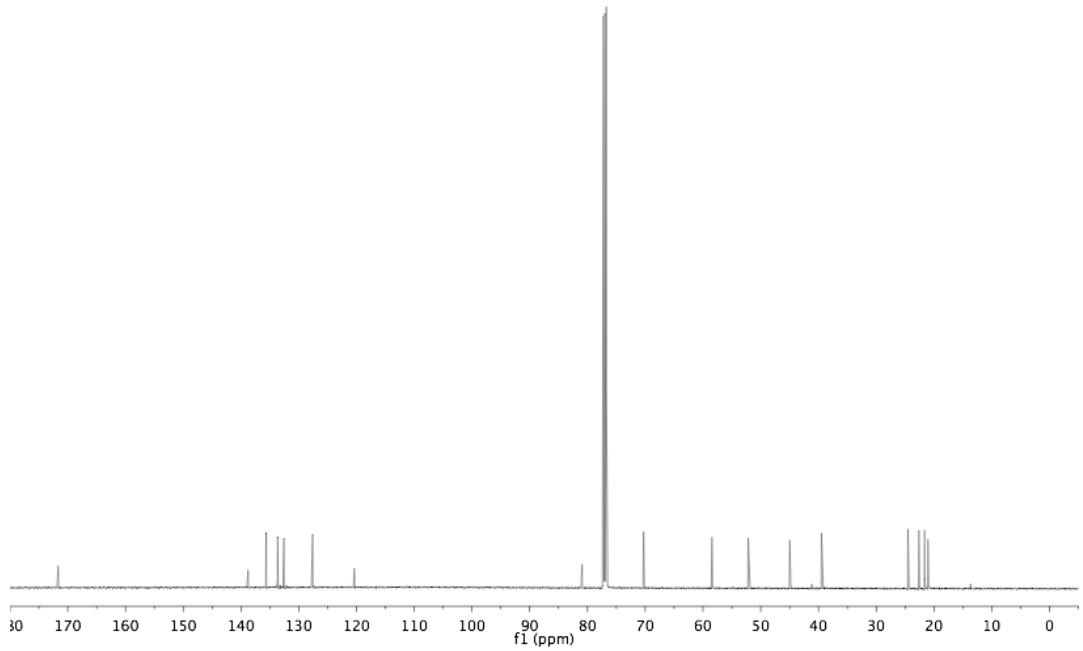
(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.53)



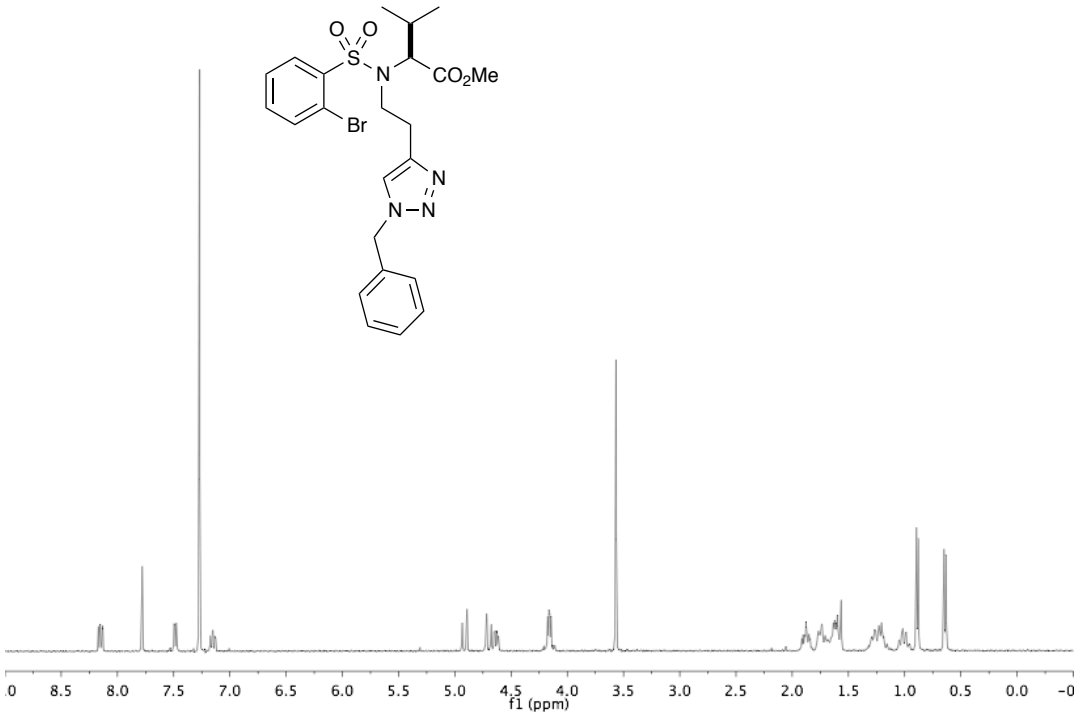


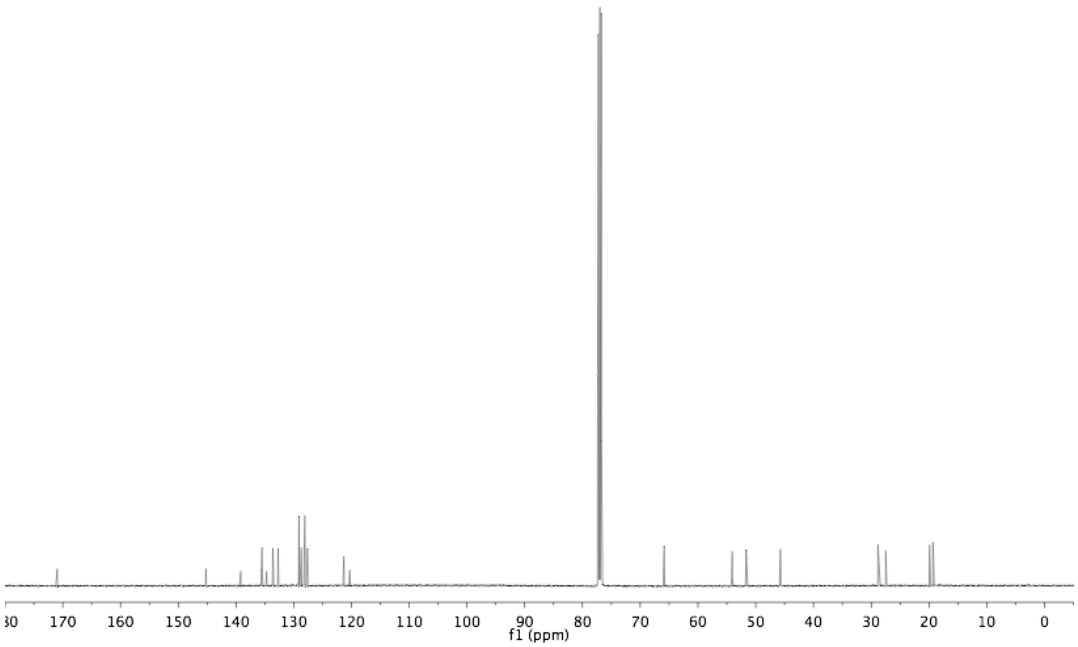
(*S*)-Methyl 2-(2-bromo-*N*-(but-3-yn-1-yl)phenylsulfonamido)-4-methylpentanoate (4.54)



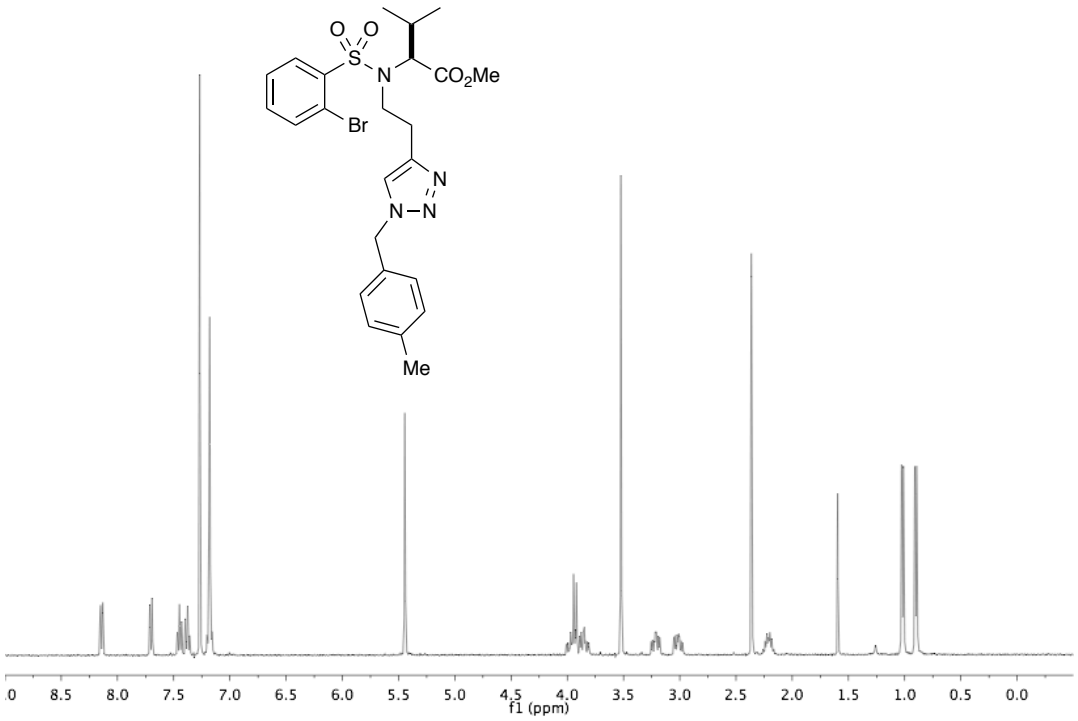


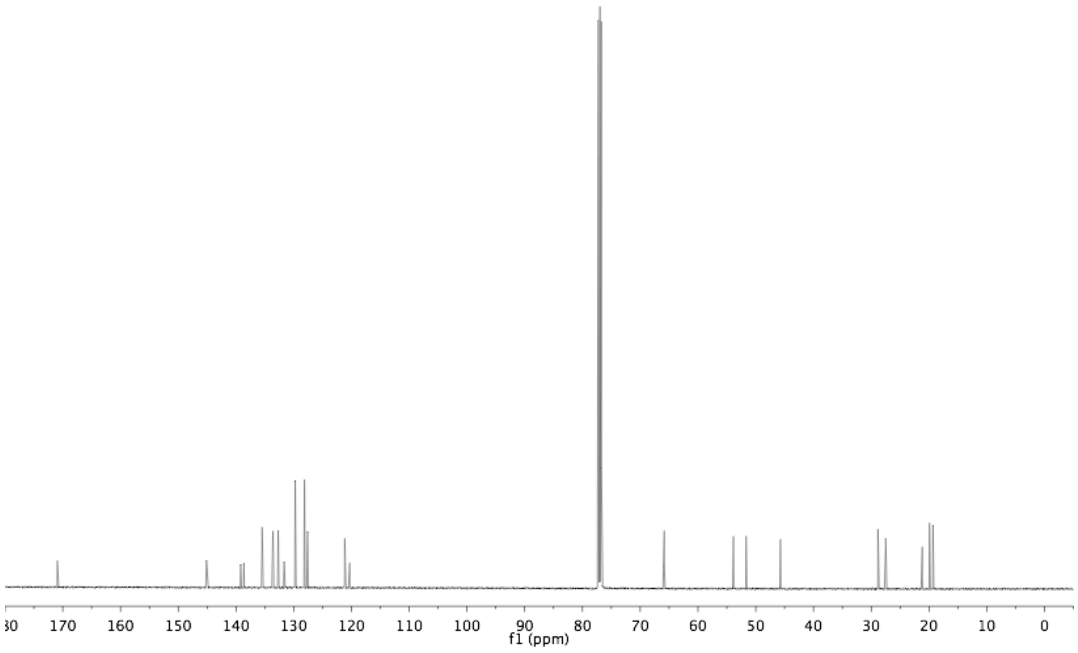
(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.55)



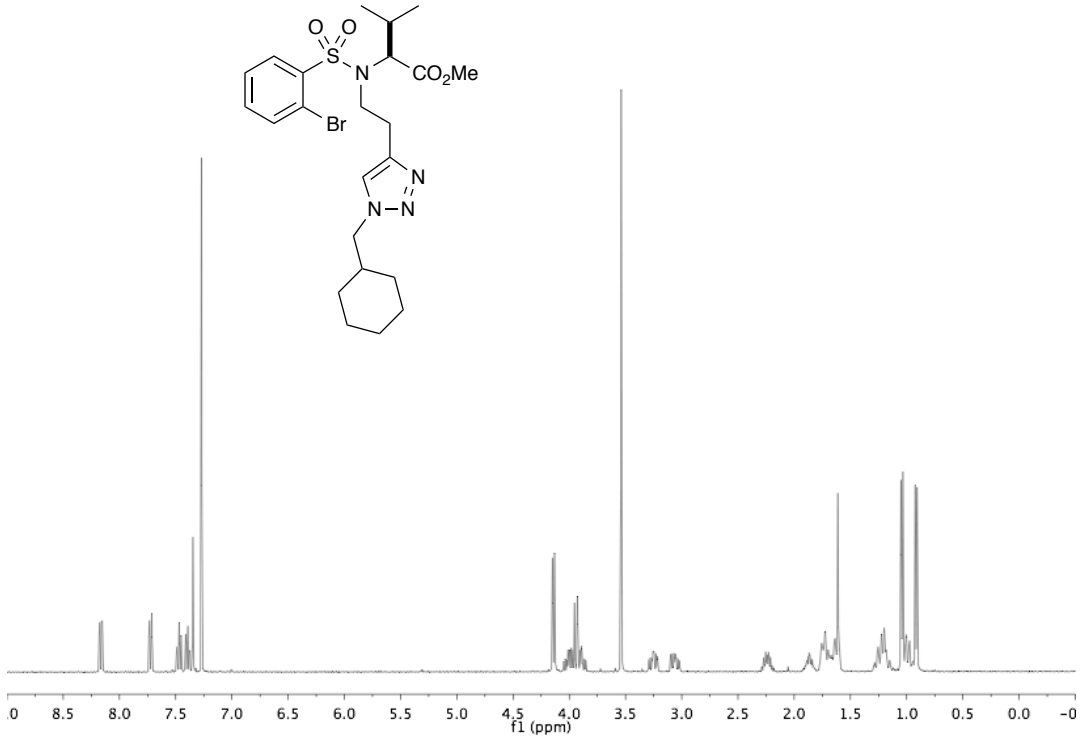


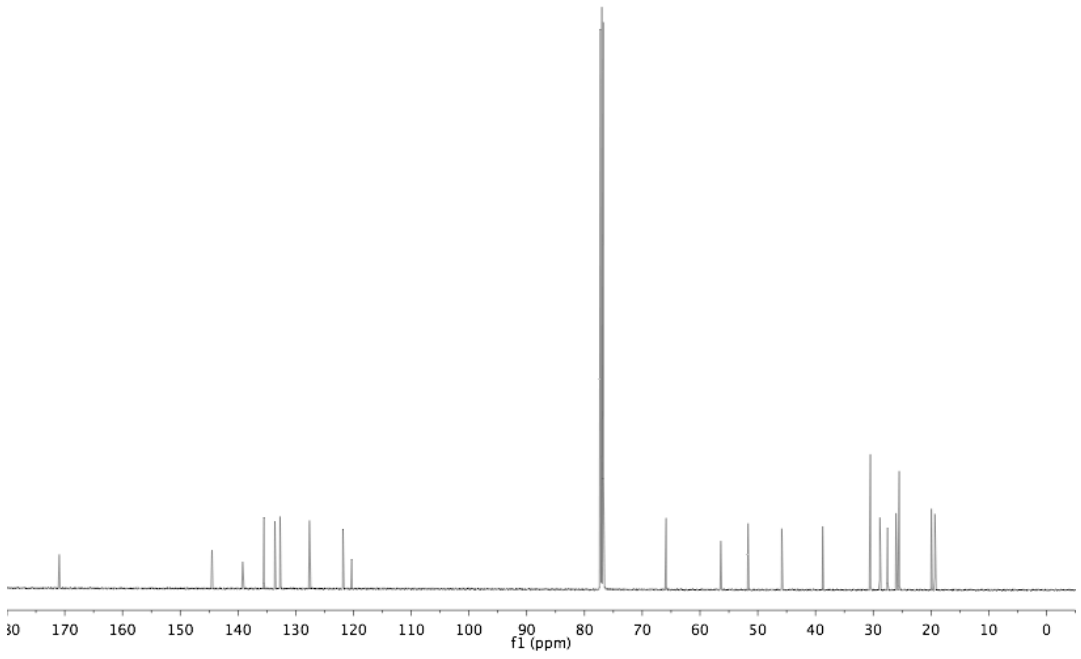
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.56)



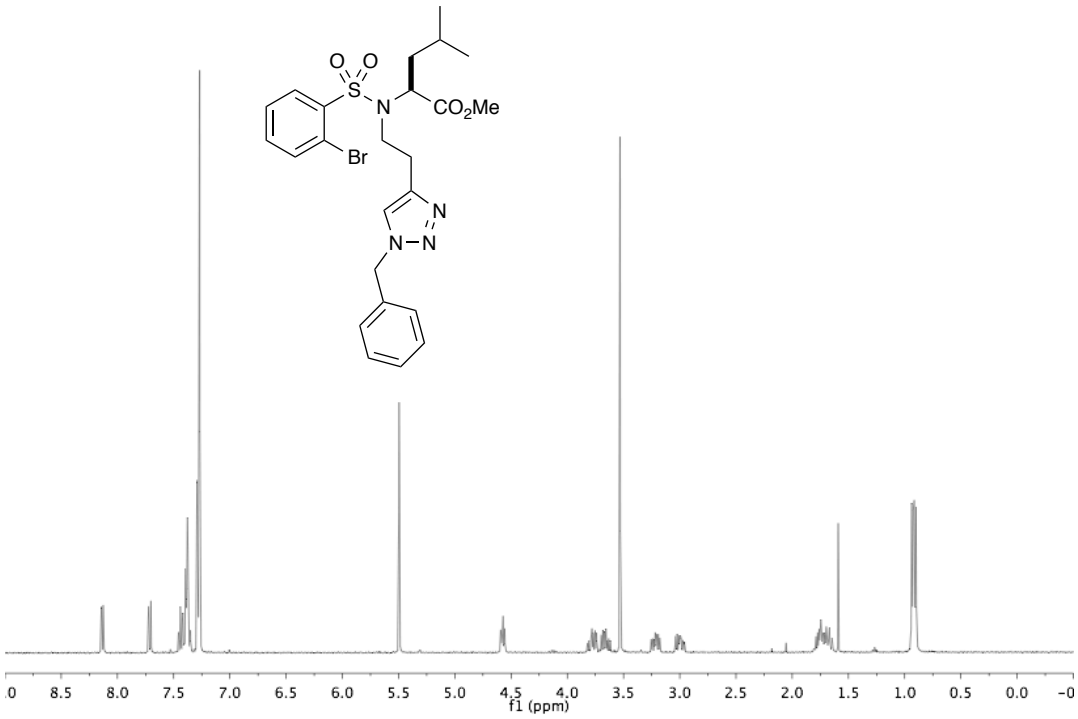


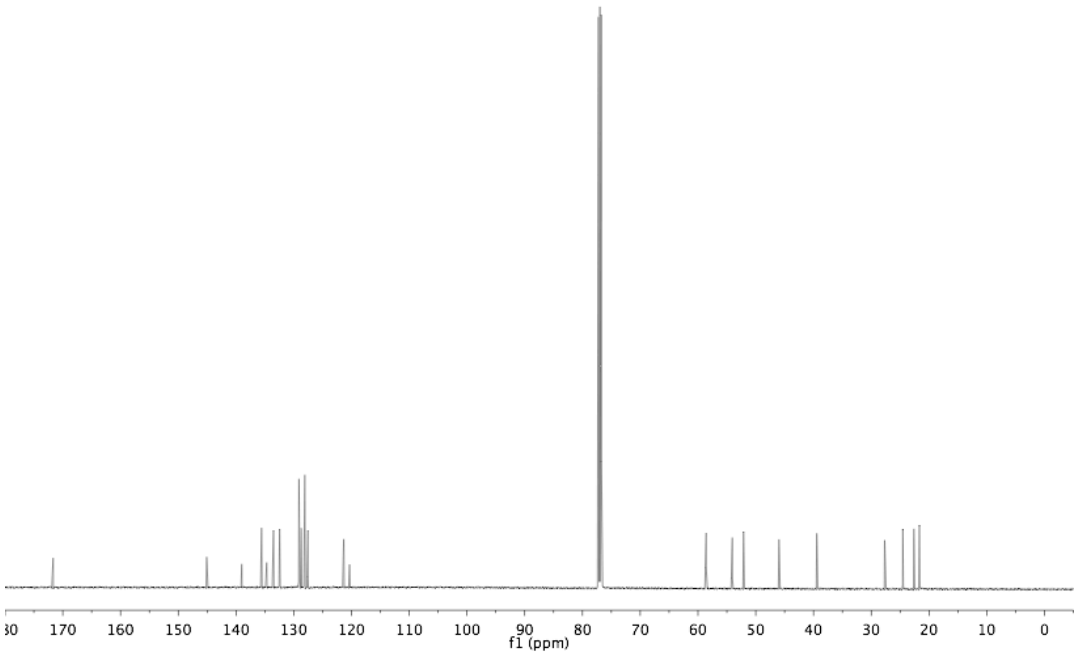
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.57)



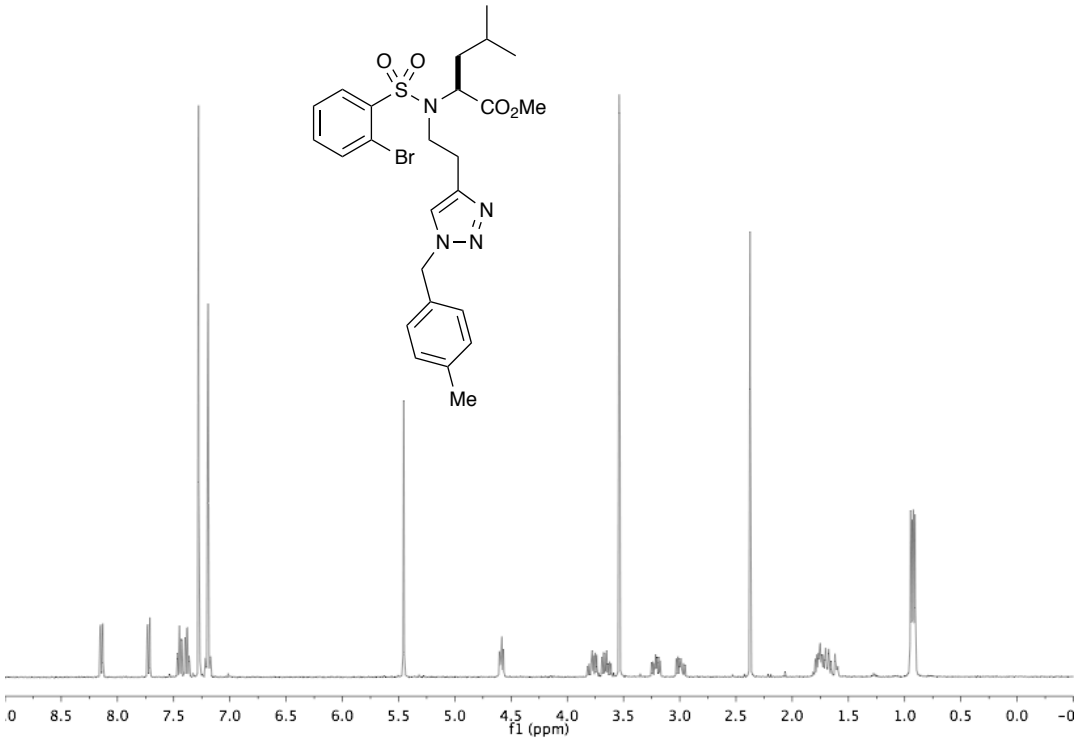


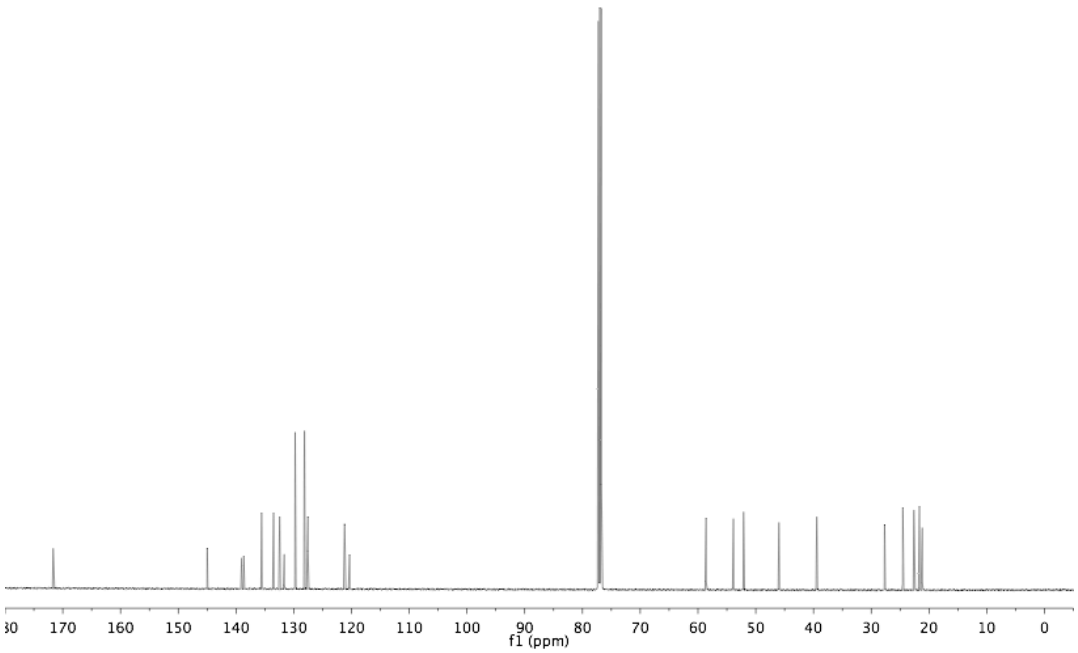
(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromophenylsulfonamido)-4-methylpentanoate (4.58)



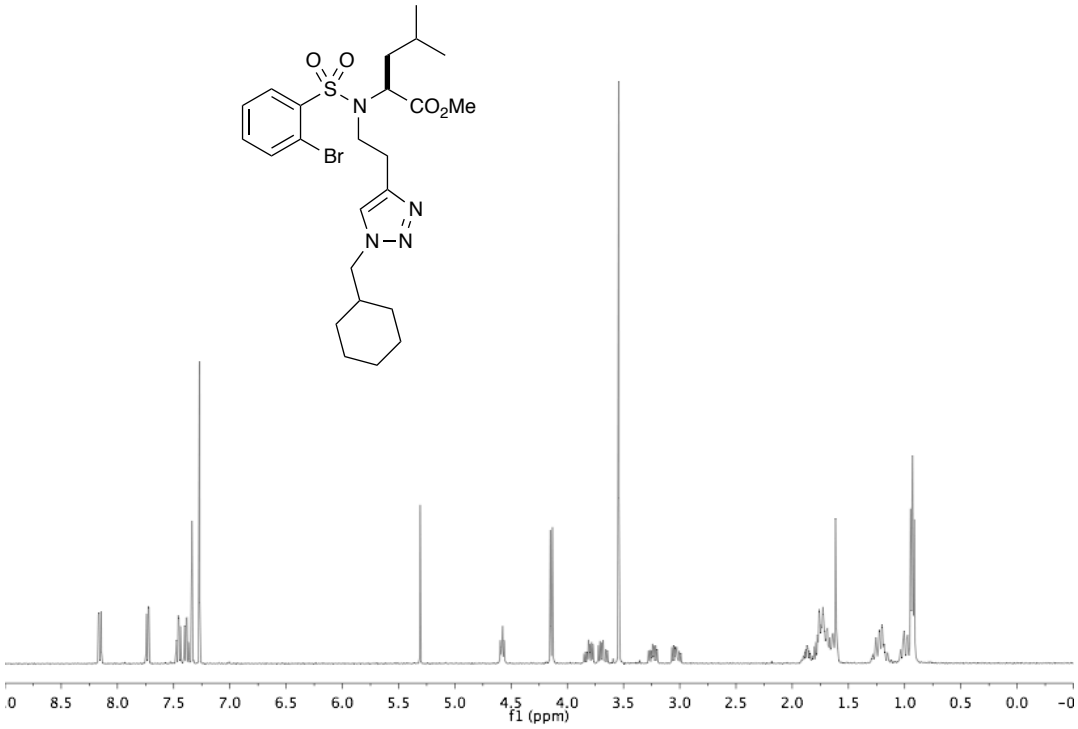


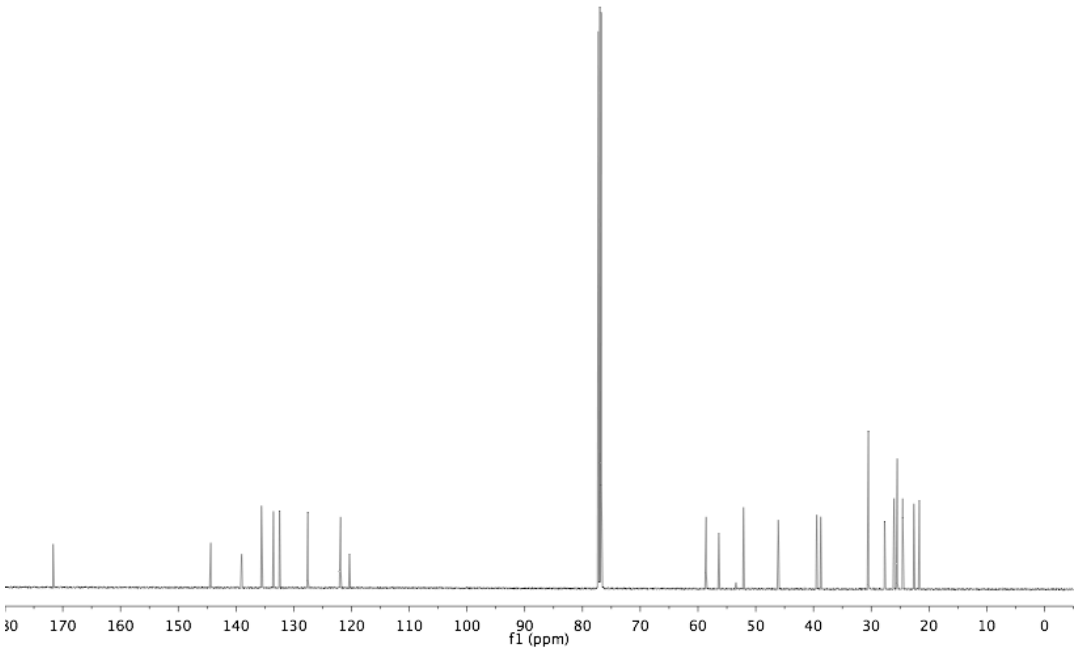
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.59)



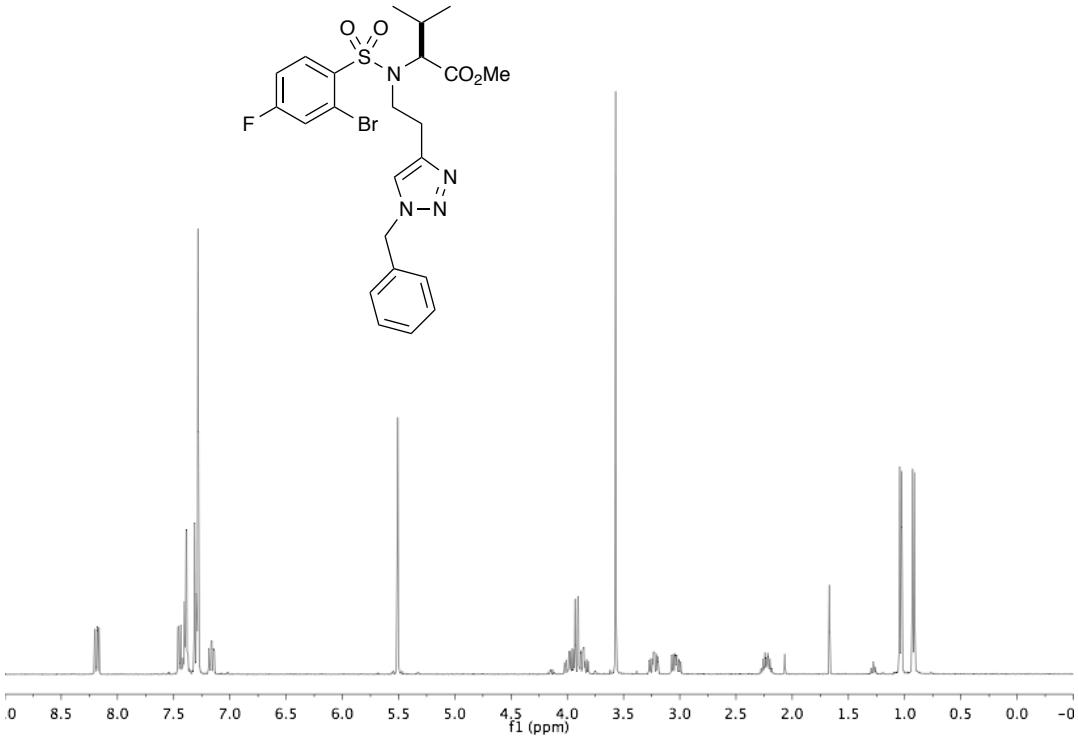


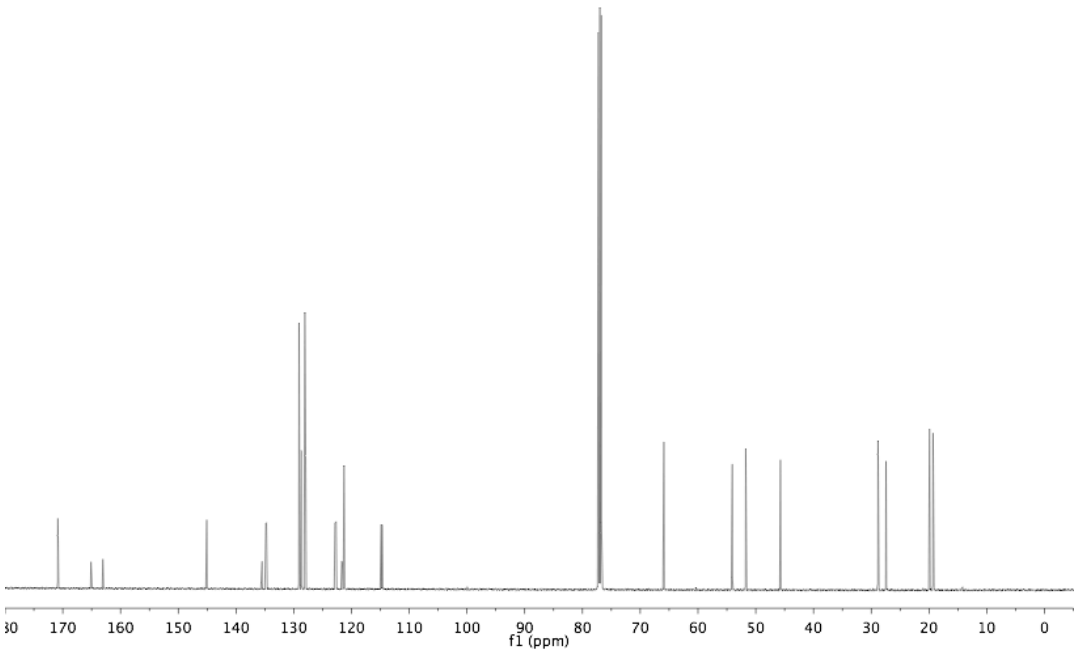
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.60)



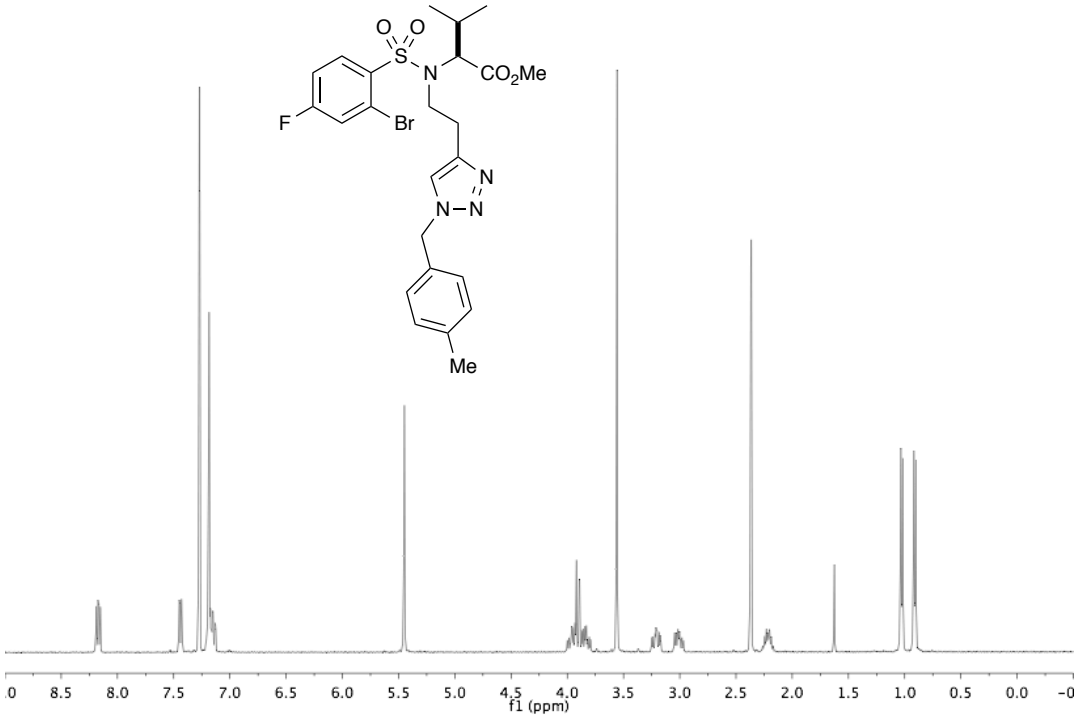


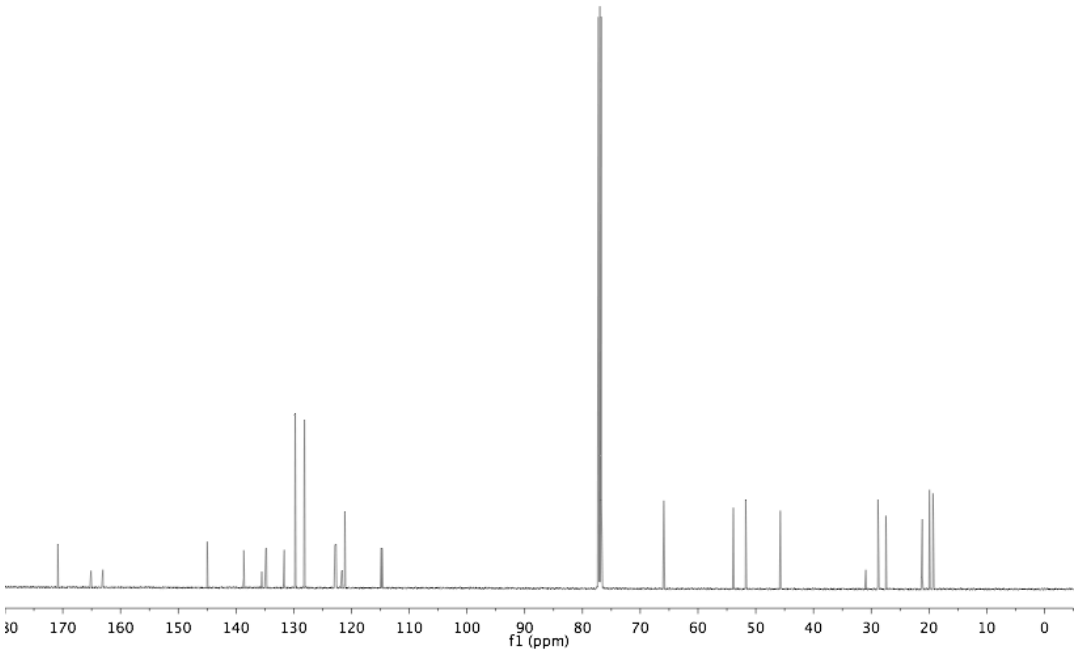
(*S*)-Methyl 2-(*N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-2-bromo-4-fluorophenylsulfonamido)-3-methylbutanoate (4.61)



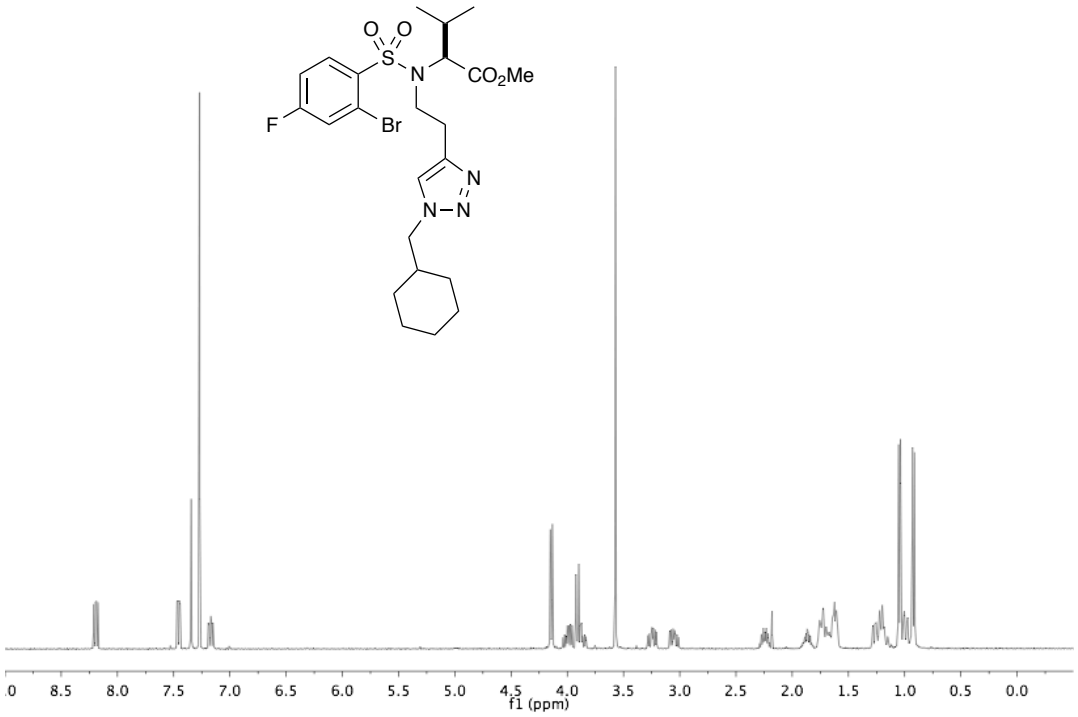


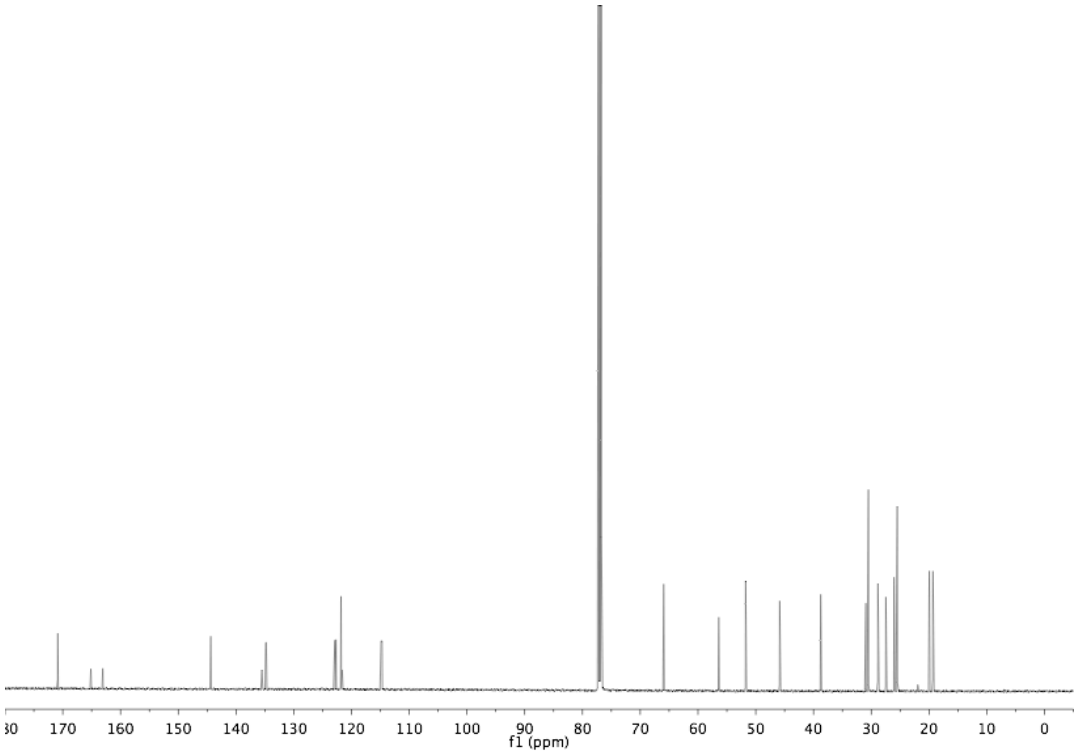
(*S*)-Methyl 2-(2-bromo-4-fluoro-*N*-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.62)



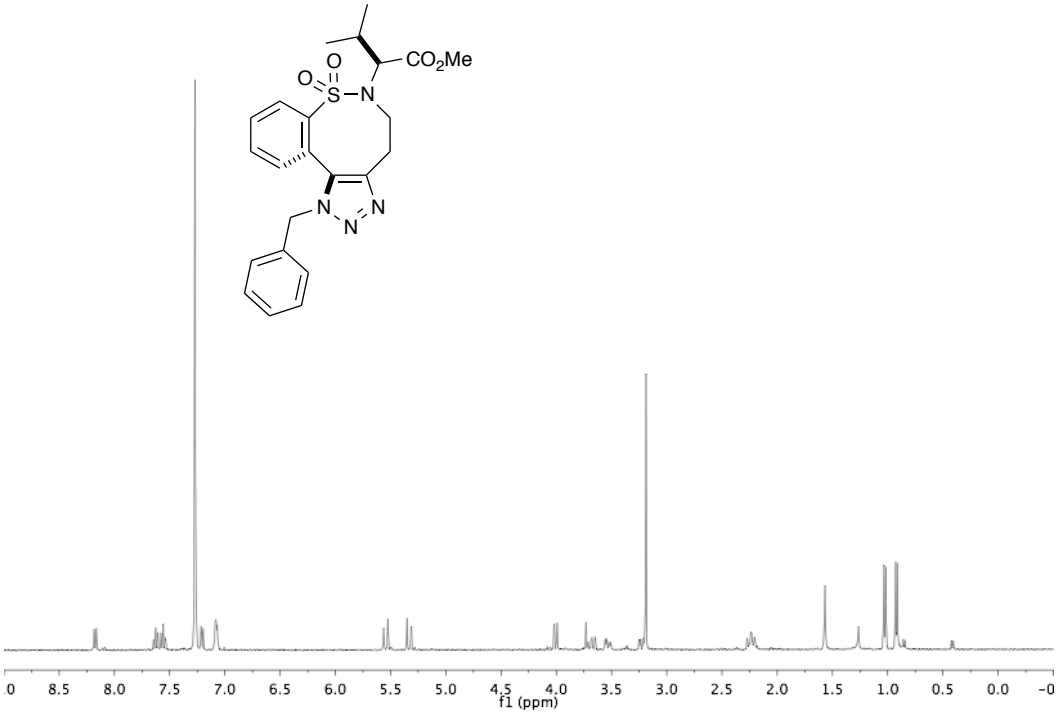


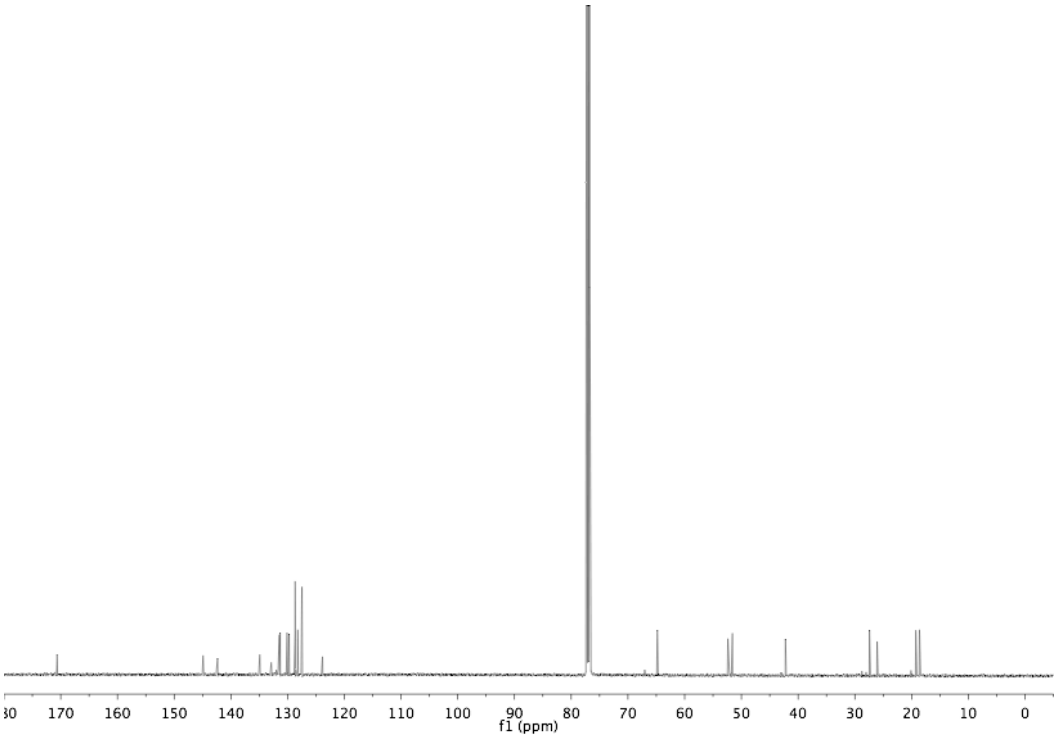
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)ethyl)-4-fluorophenylsulfonamido)-3-methylbutanoate (4.63)



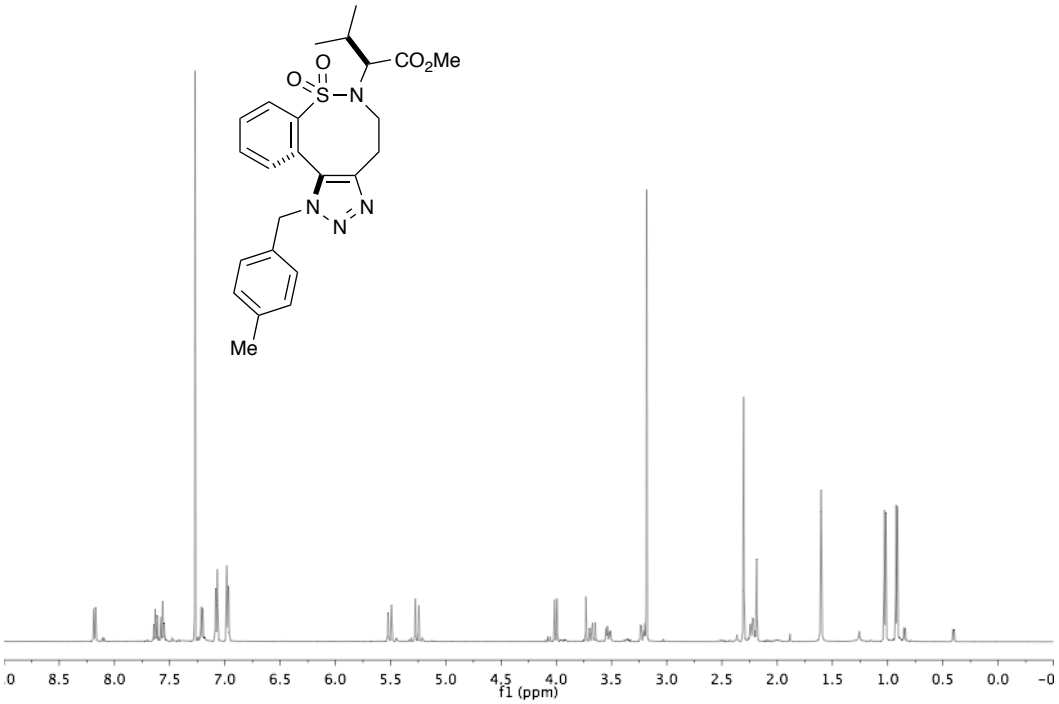


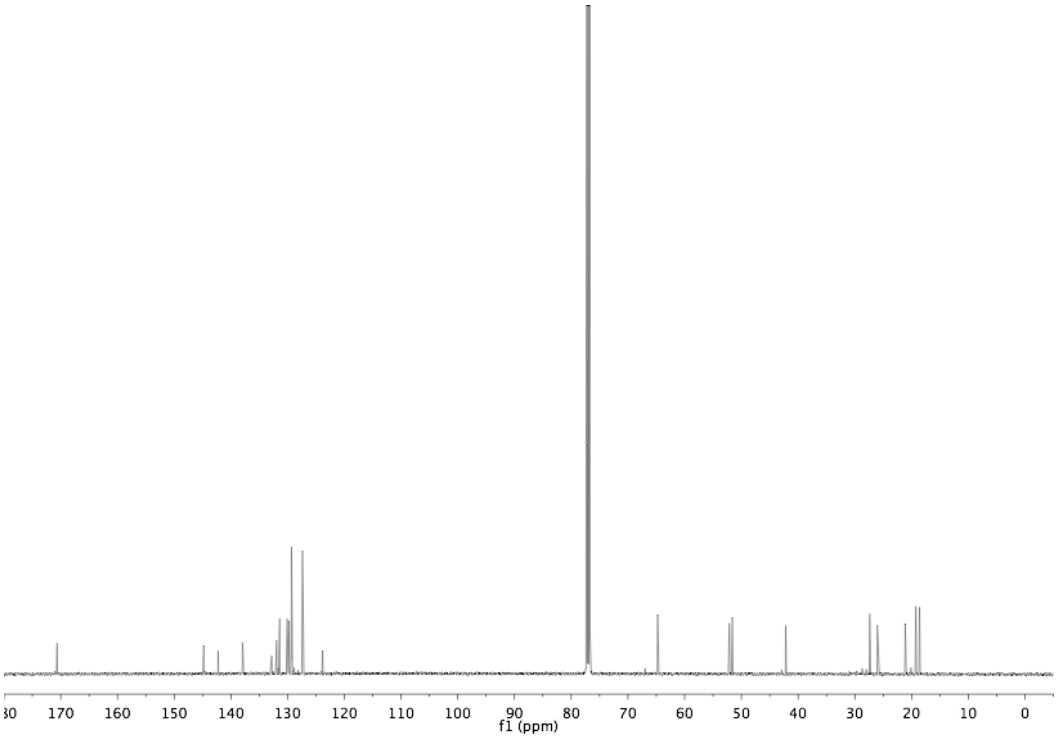
(*S*)-Methyl 2-(1-benzyl-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.64)



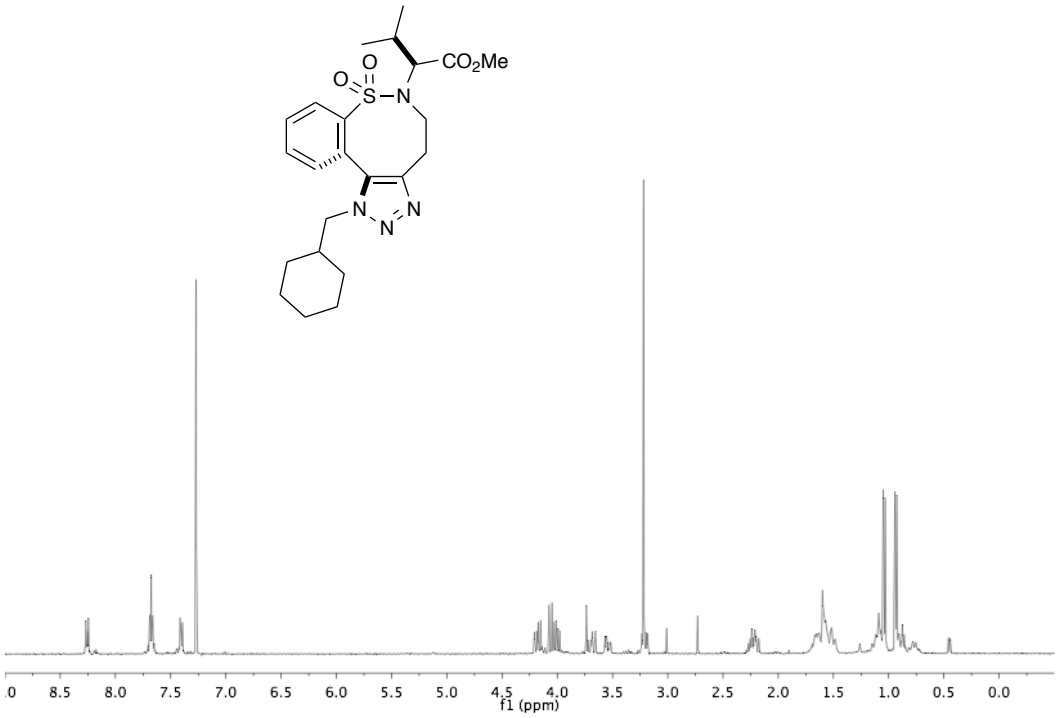


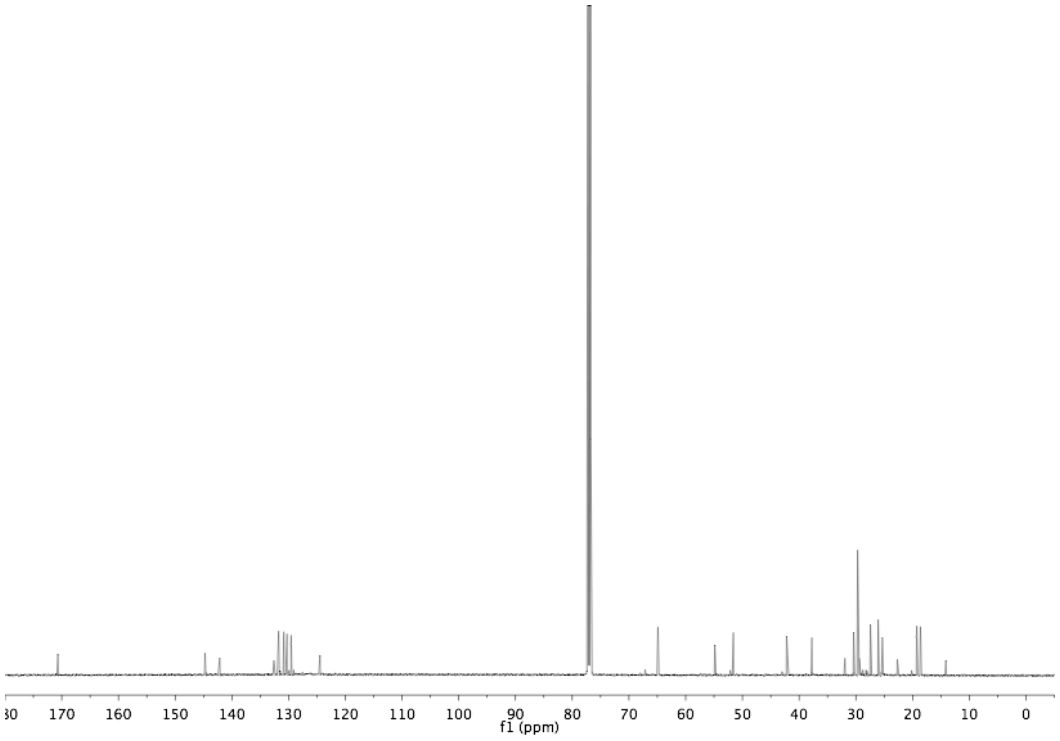
(*S*)-Methyl 3-methyl-2-(1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)butanoate (4.65)



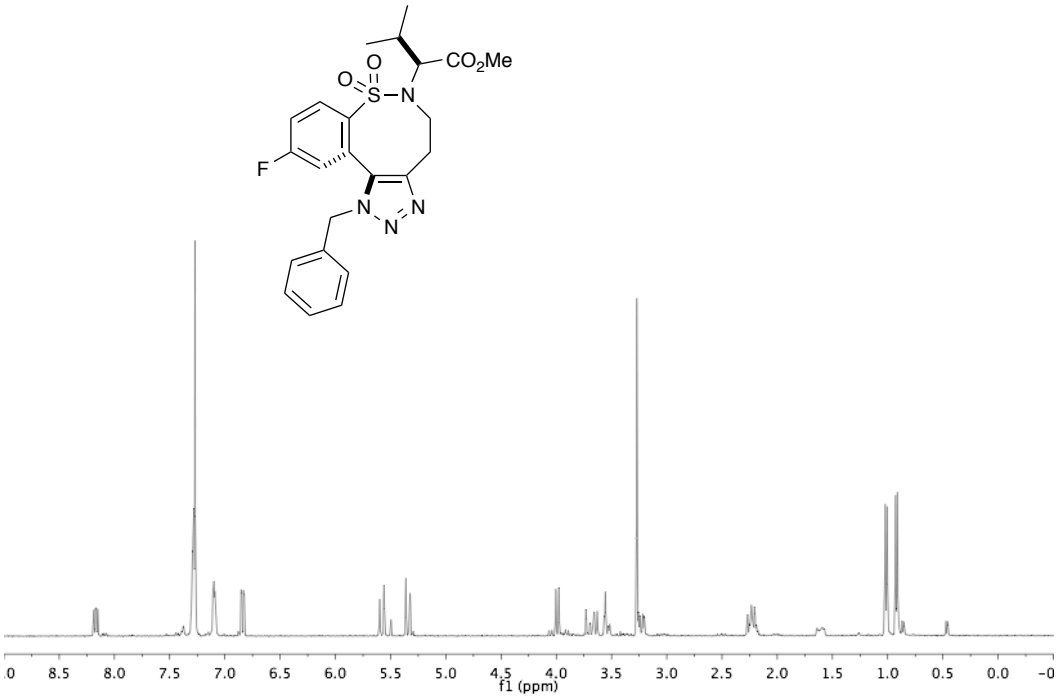


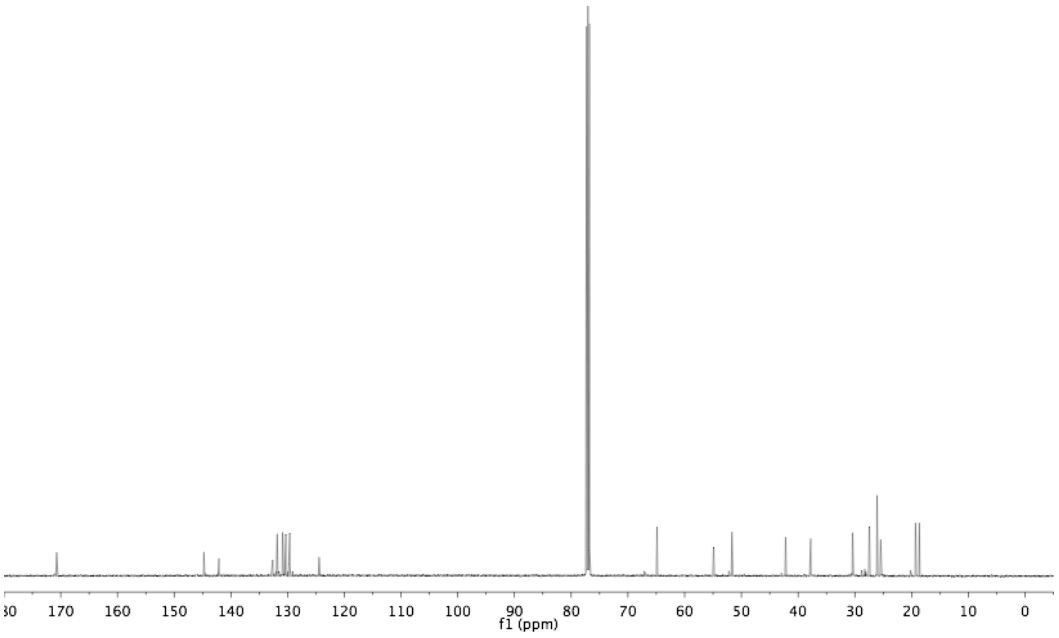
(*S*)-Methyl 2-(1-(cyclohexylmethyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.66)



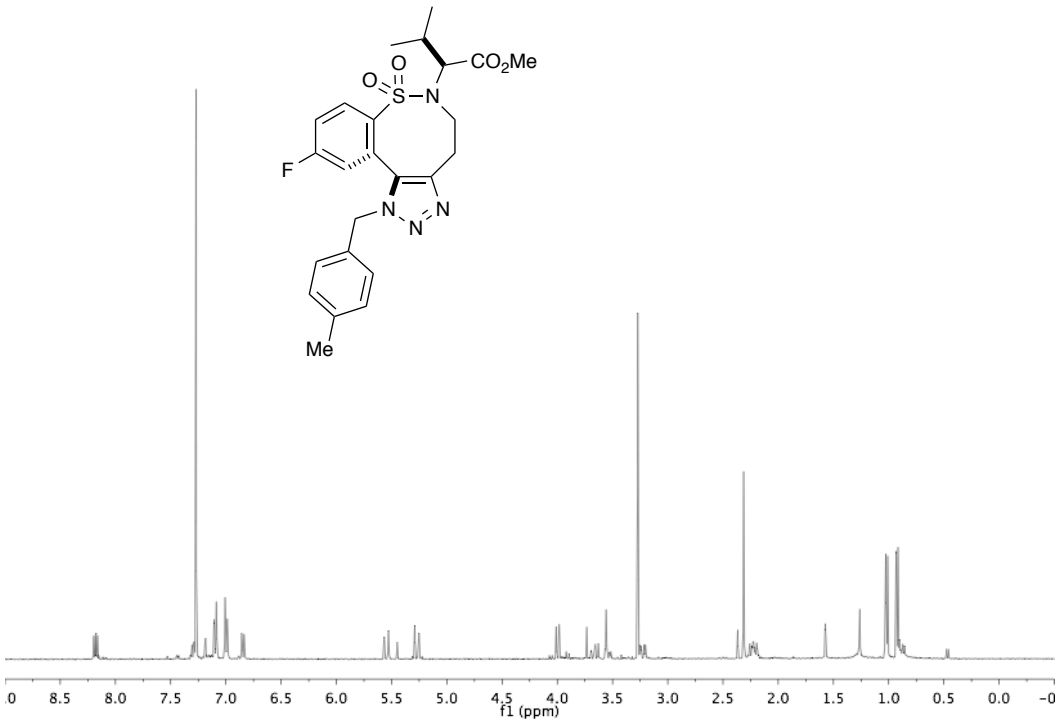


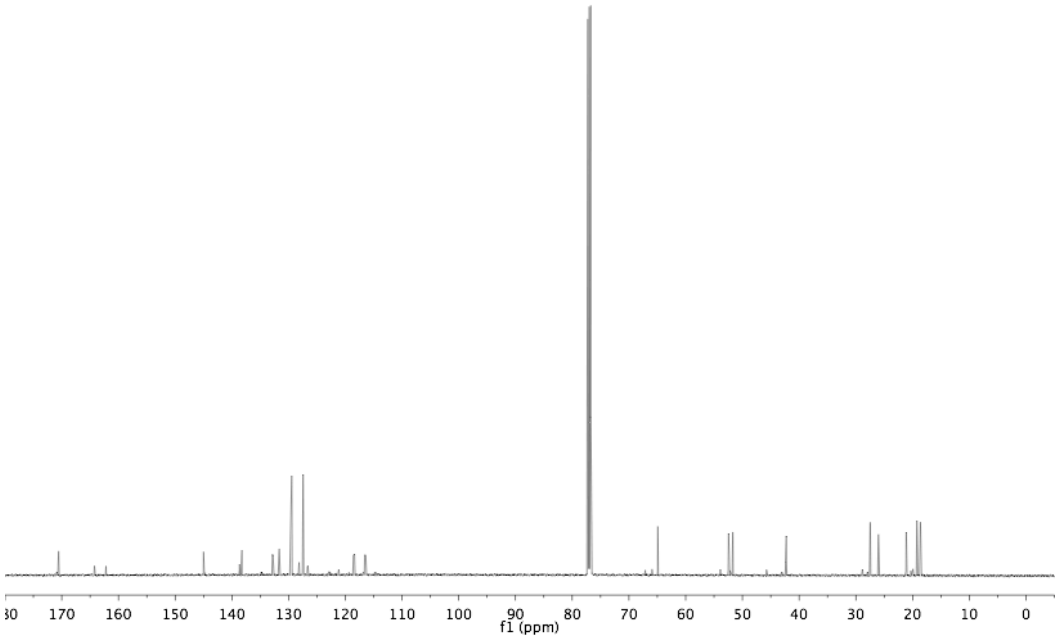
(*S*)-Methyl 2-(1-benzyl-10-fluoro-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.67)



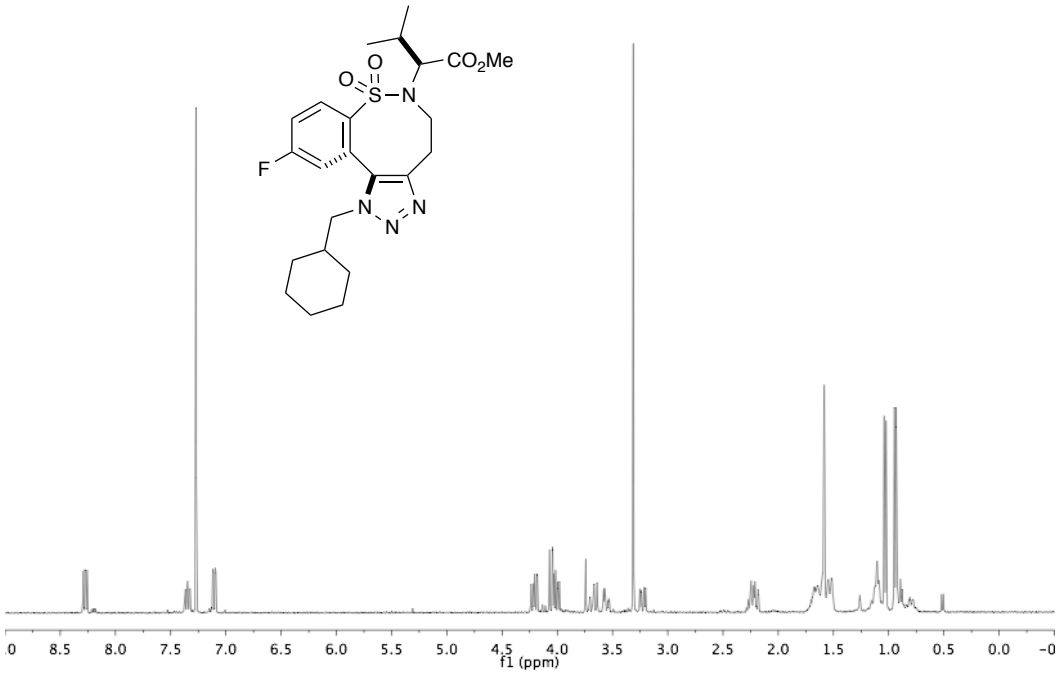


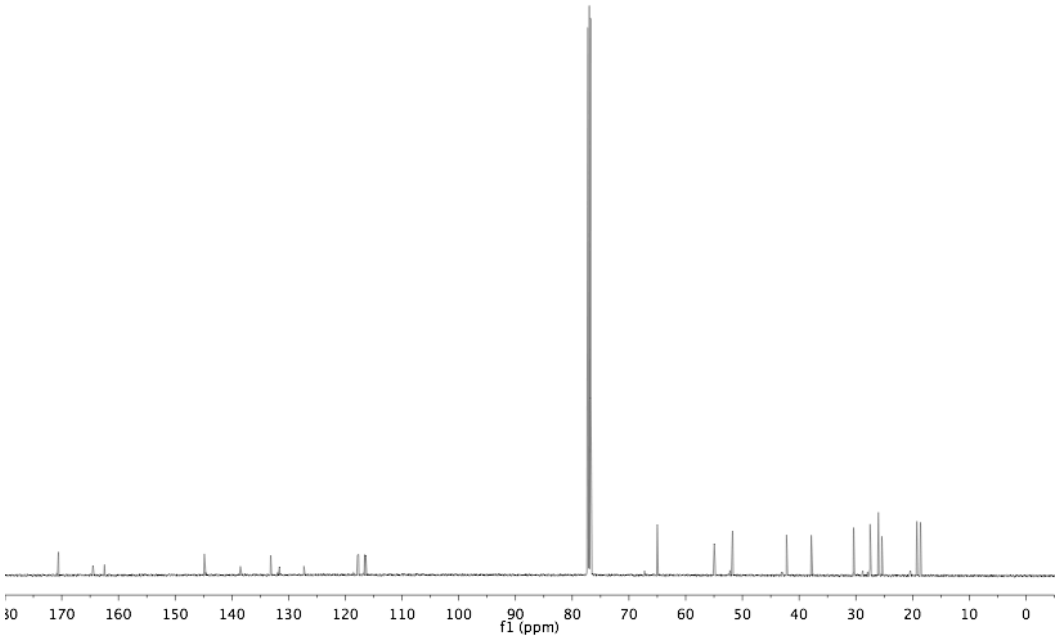
(*S*)-Methyl 2-(10-fluoro-1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.68)



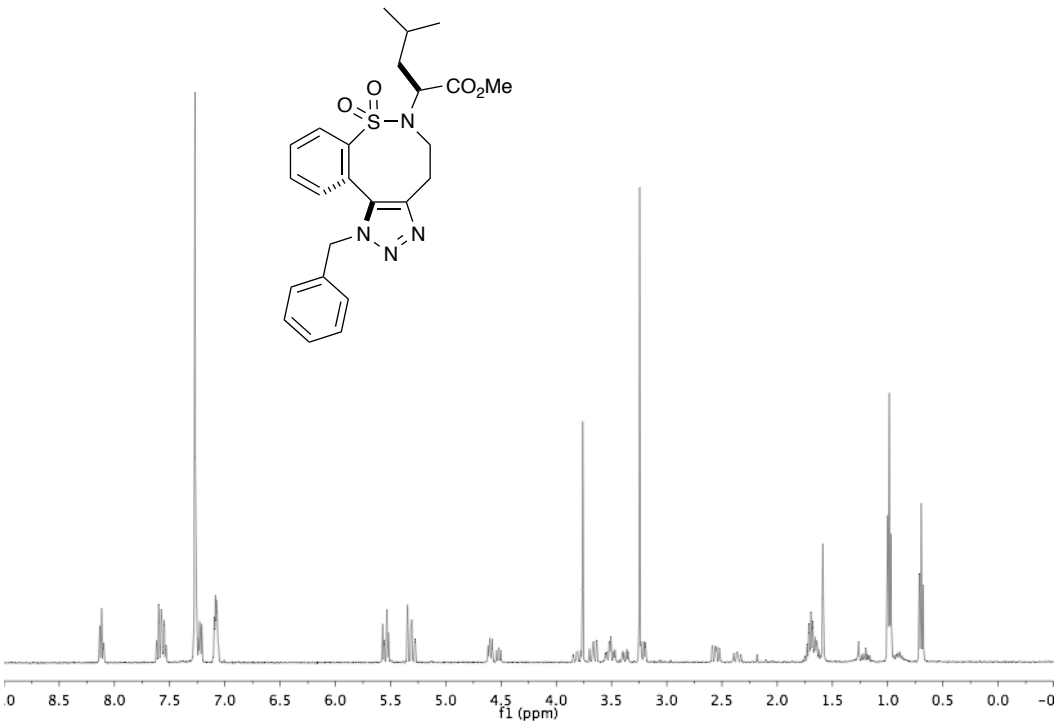


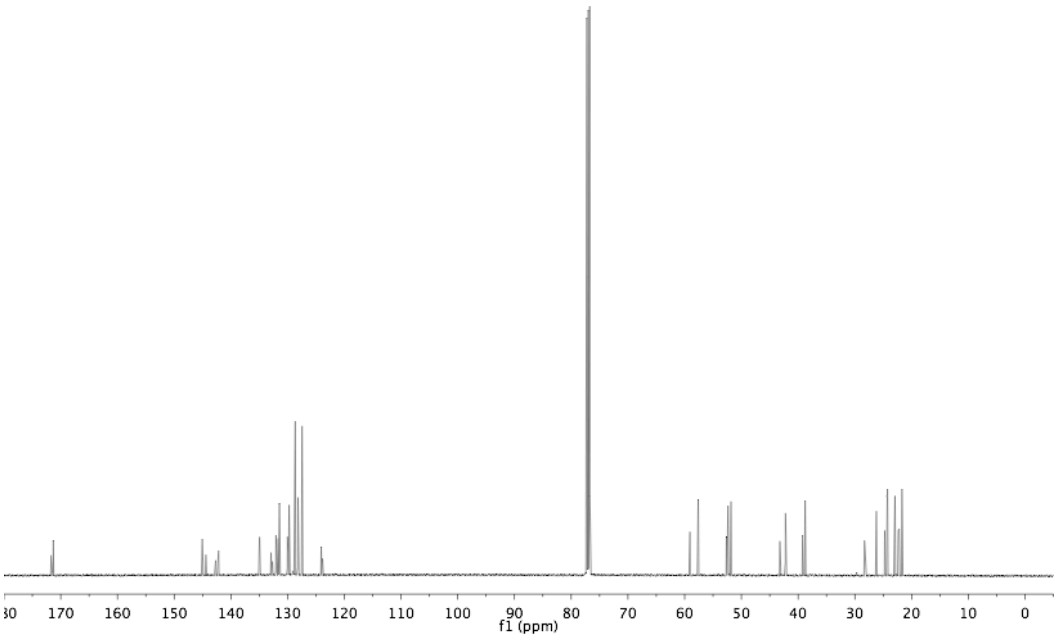
(*S*)-Methyl 2-(1-(cyclohexylmethyl)-10-fluoro-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.69)



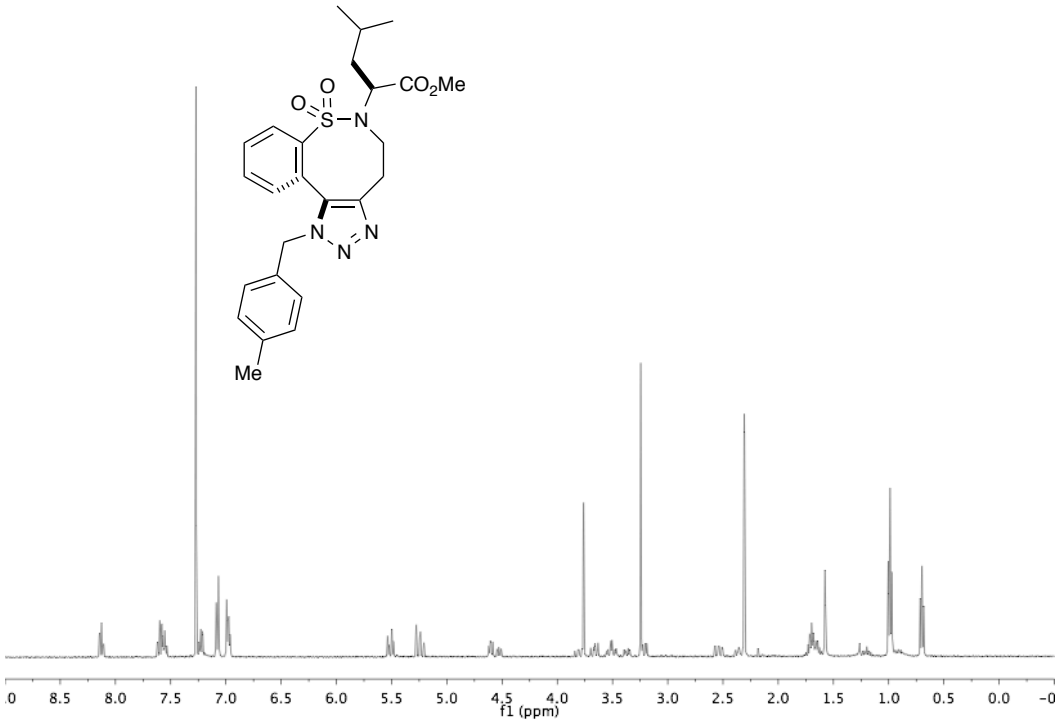


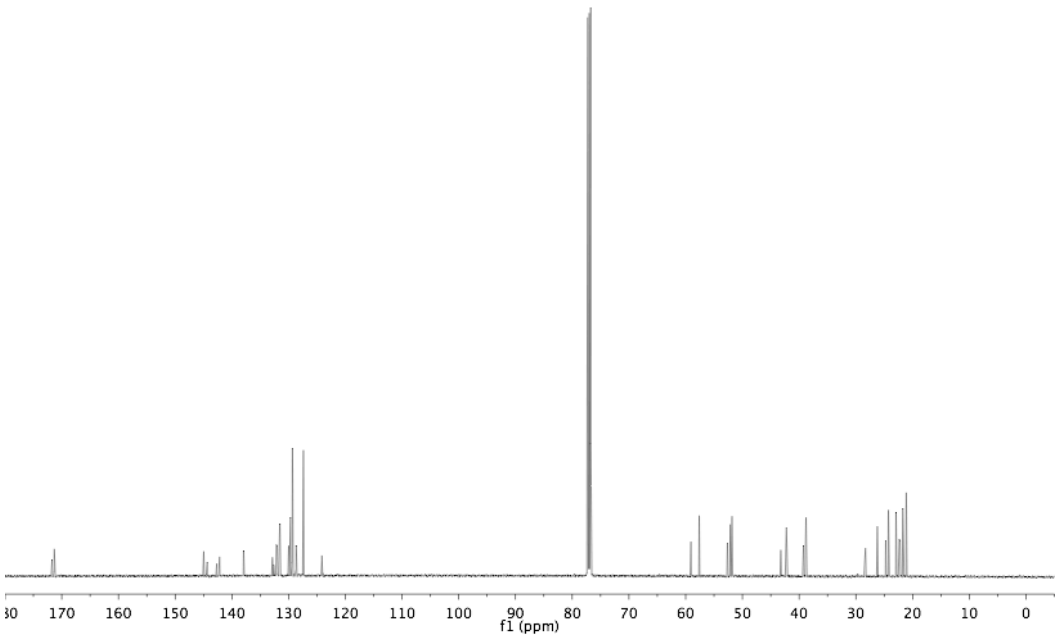
(*S*)-Methyl 2-(1-benzyl-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.70)



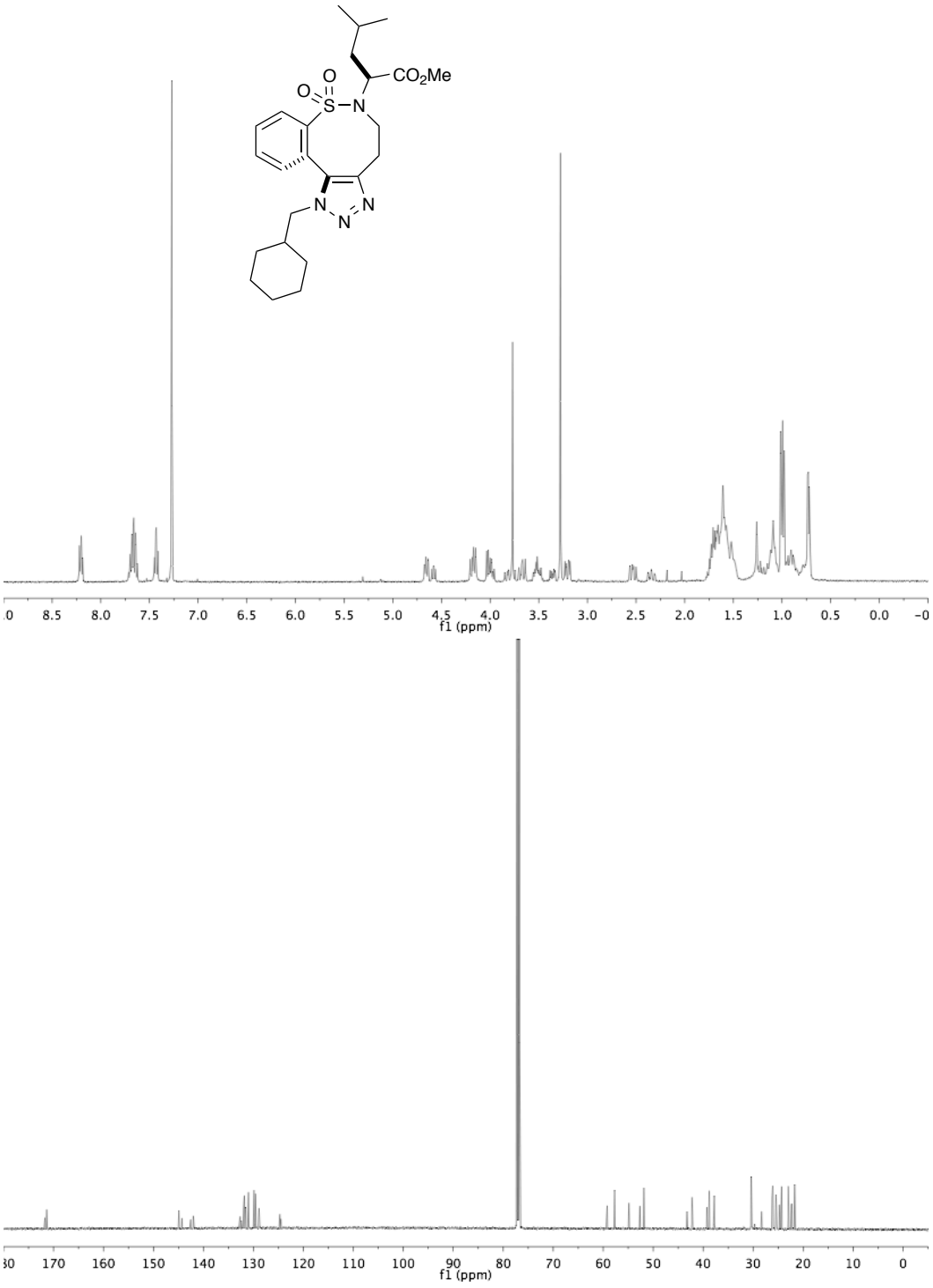


(*S*)-Methyl 4-methyl-2-(1-(4-methylbenzyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)pentanoate (4.71)

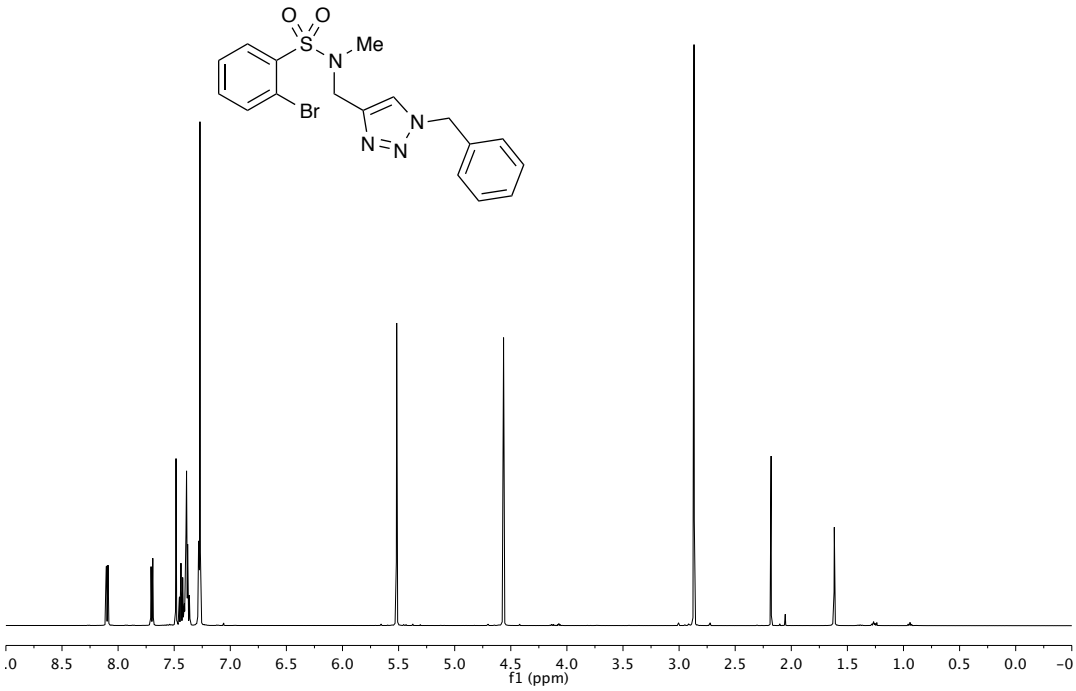


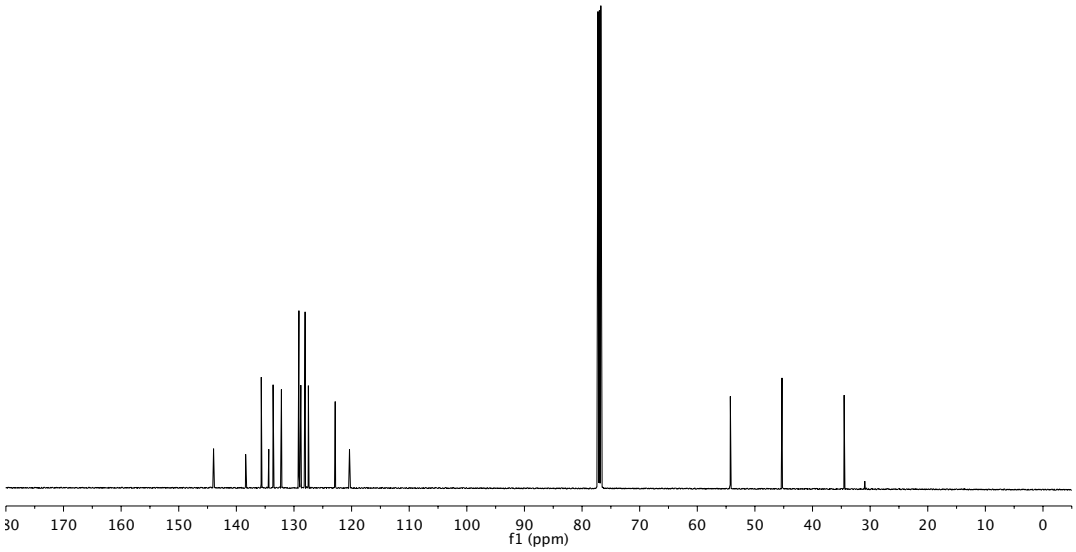


(*S*)-Methyl 2-(1-(cyclohexylmethyl)-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.72)

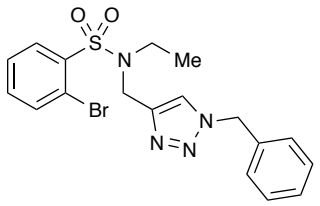


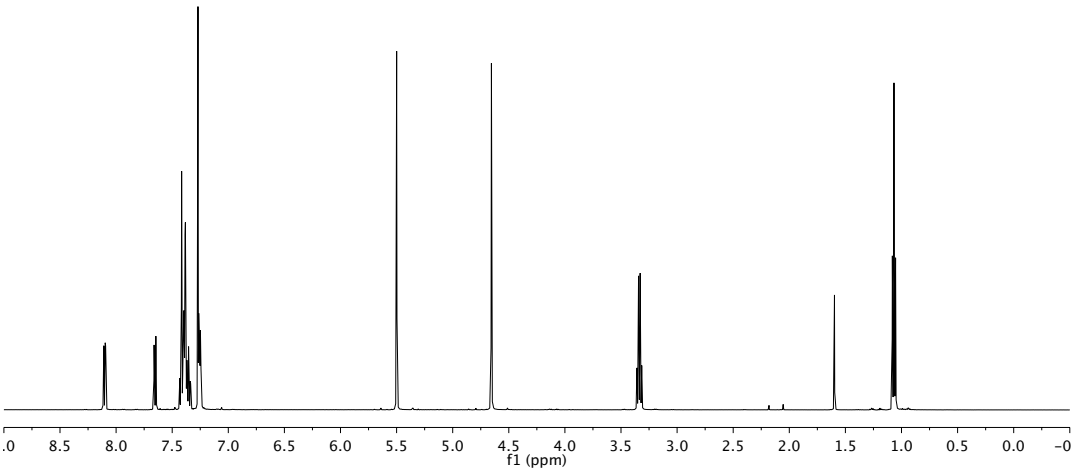
_N_-((1-Benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-2-bromo-_N_-methylbenzenesulfonamide (4.73)

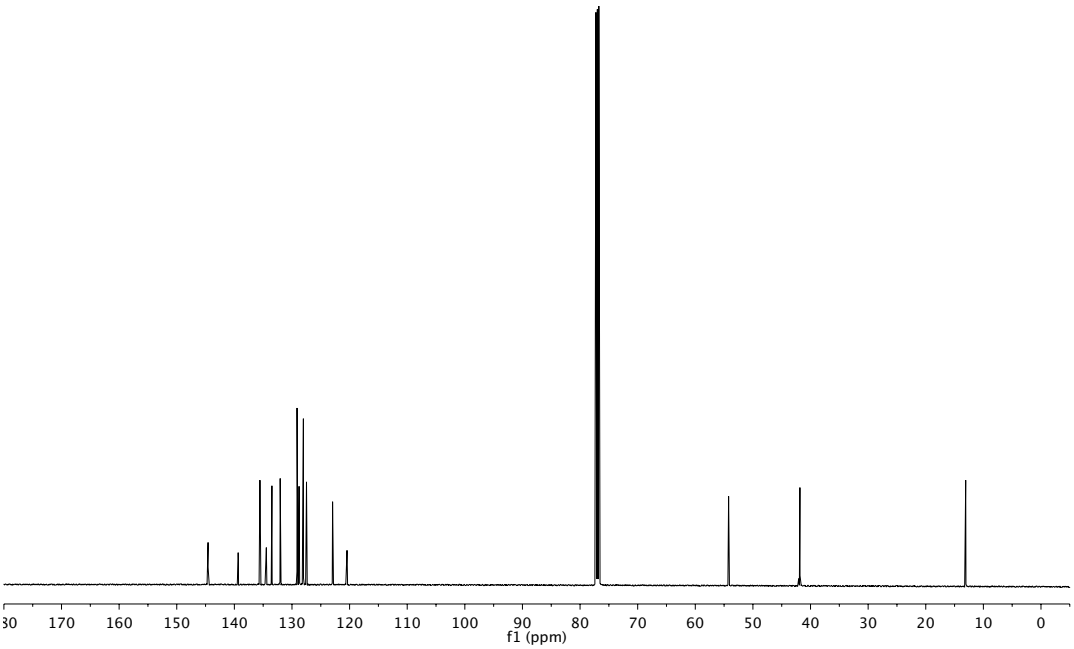




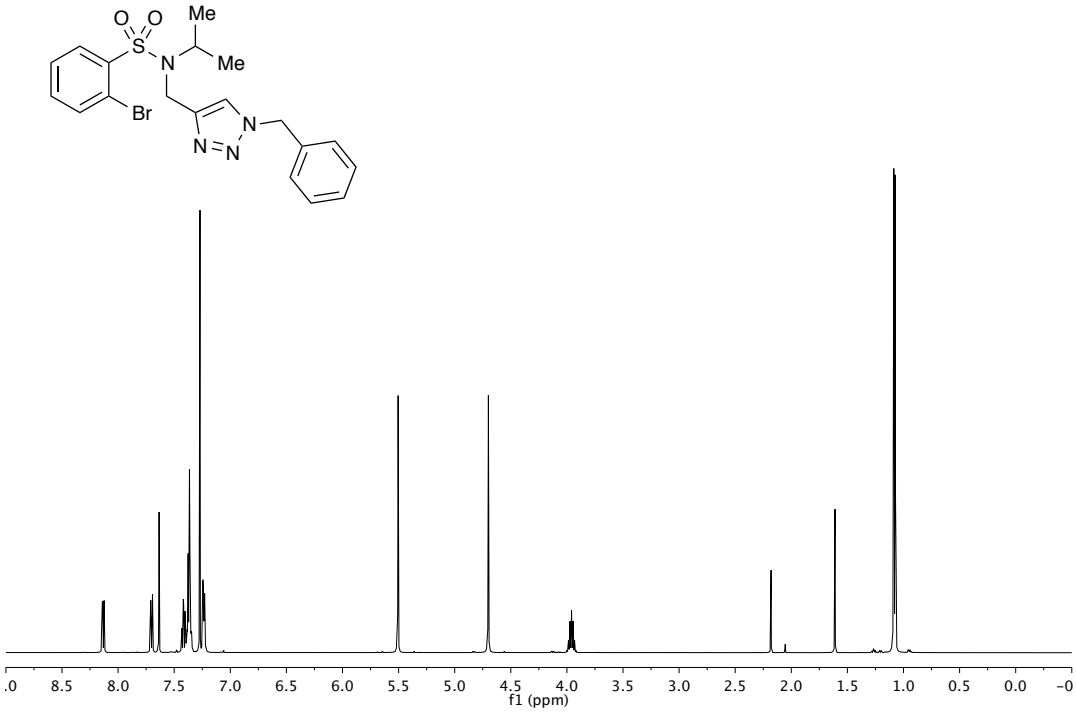
***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-ethylbenzenesulfonamide (4.74)**

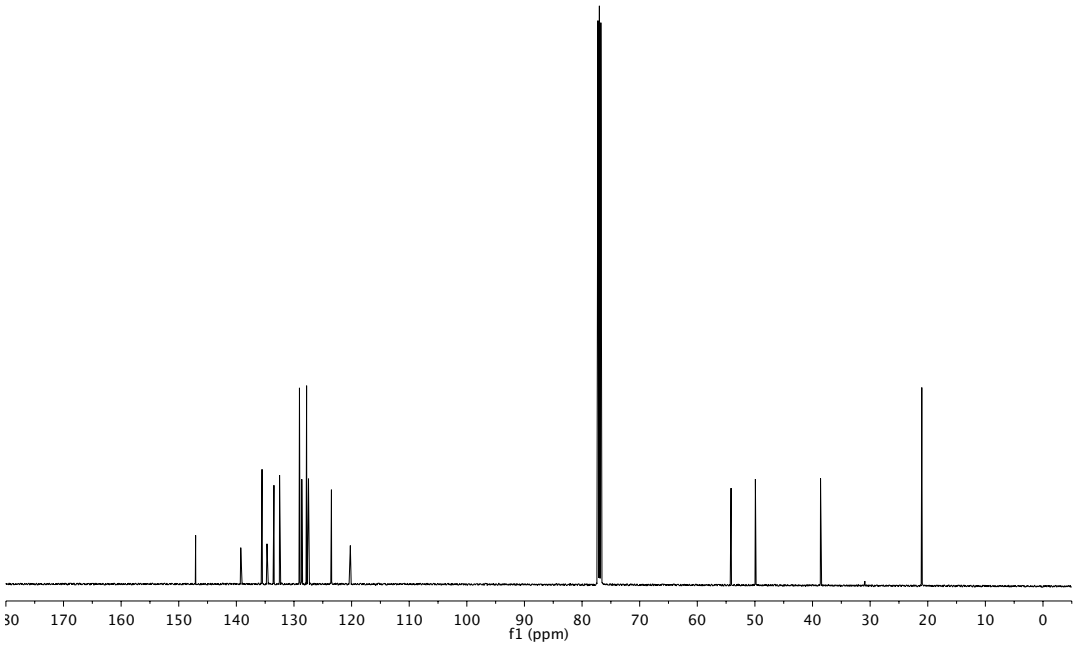




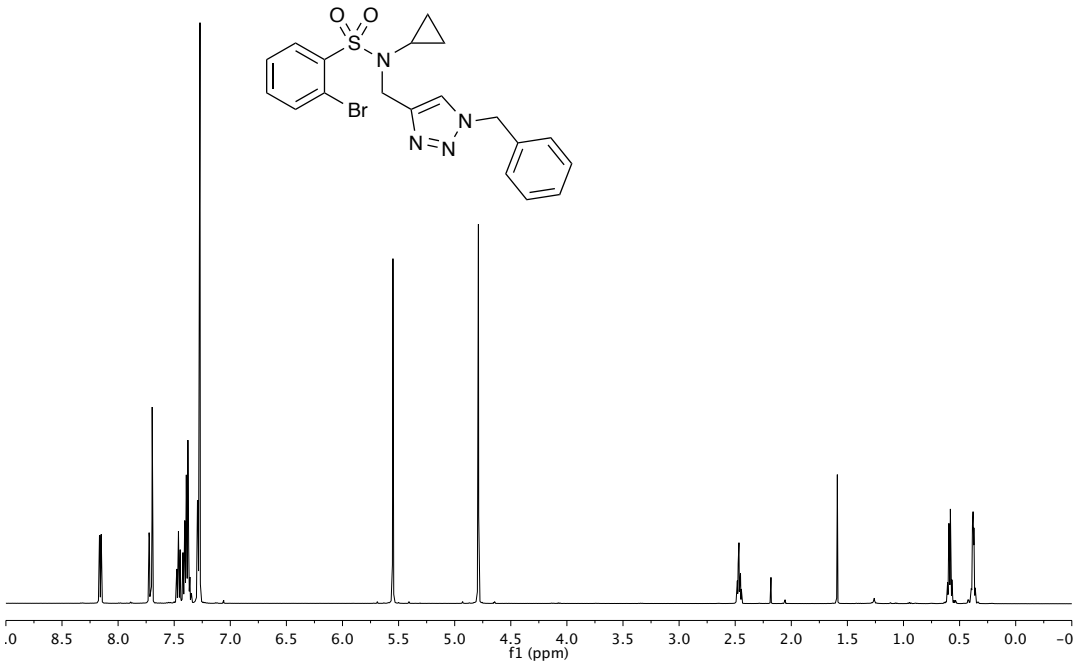


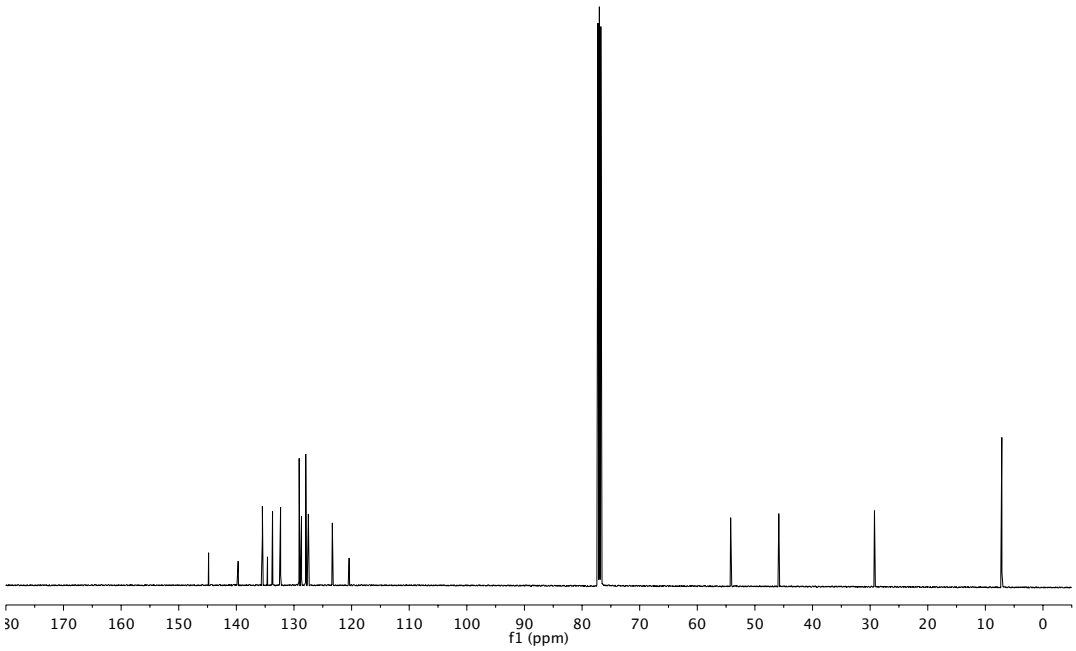
_N_-((1-Benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-2-bromo-_N_-isopropylbenzenesulfonamide (4.75)



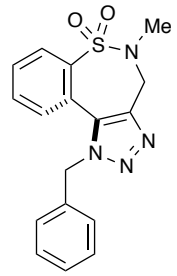


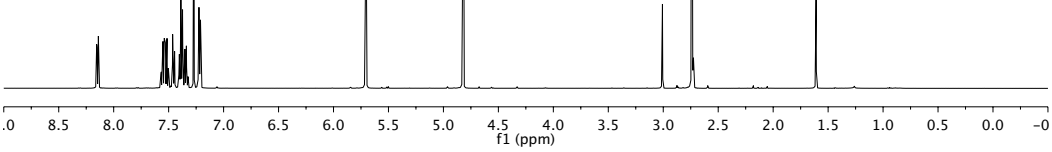
_N_-((1-Benzyl-1_H_-1,2,3-triazol-4-yl)methyl)-2-bromo-_N_-cyclopropylbenzenesulfonamide (4.76)

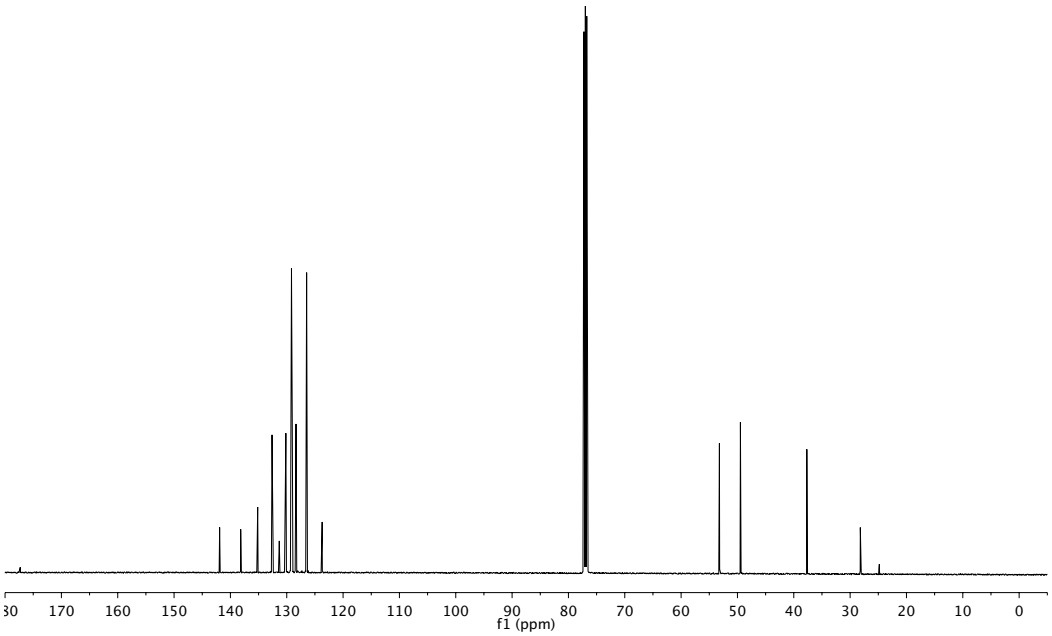




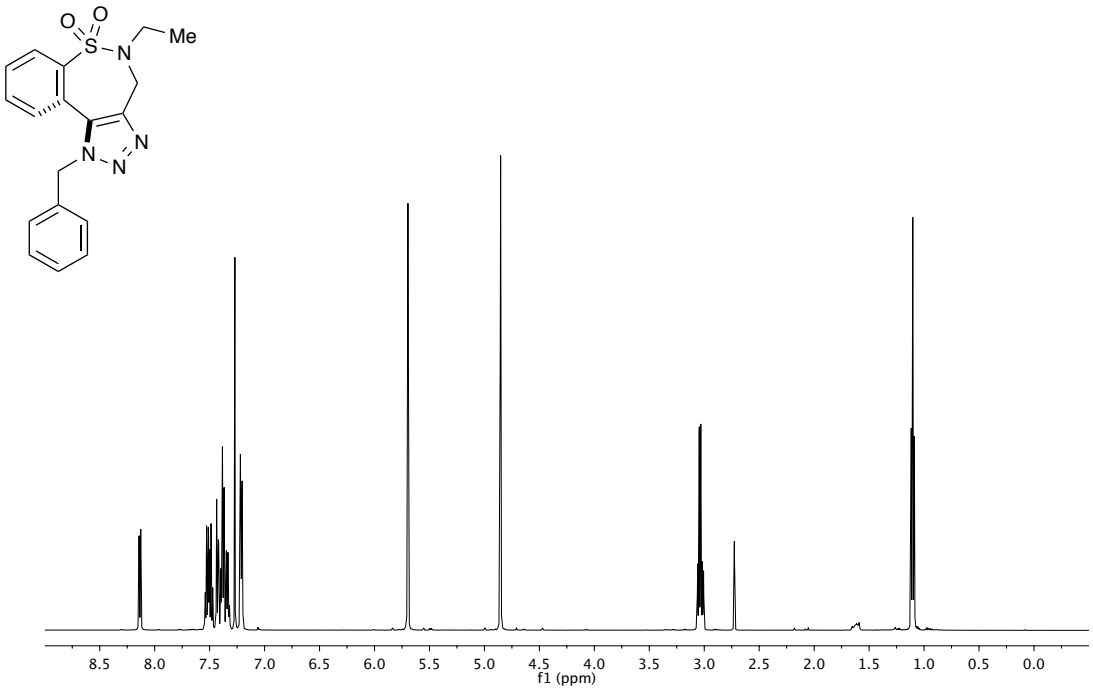
(±)-1-Benzyl-5-methyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.77)

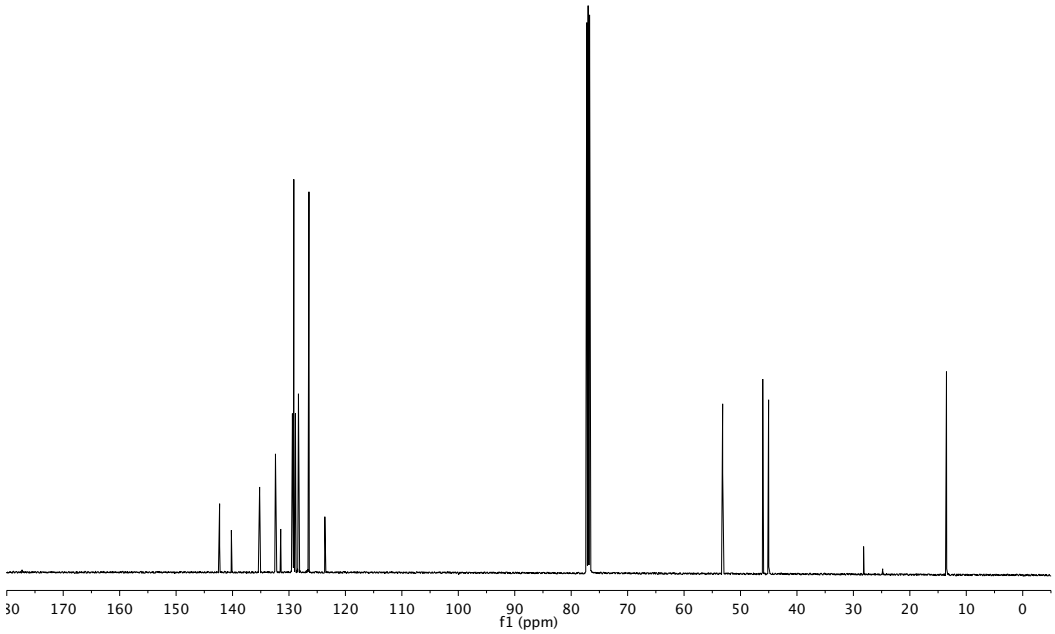




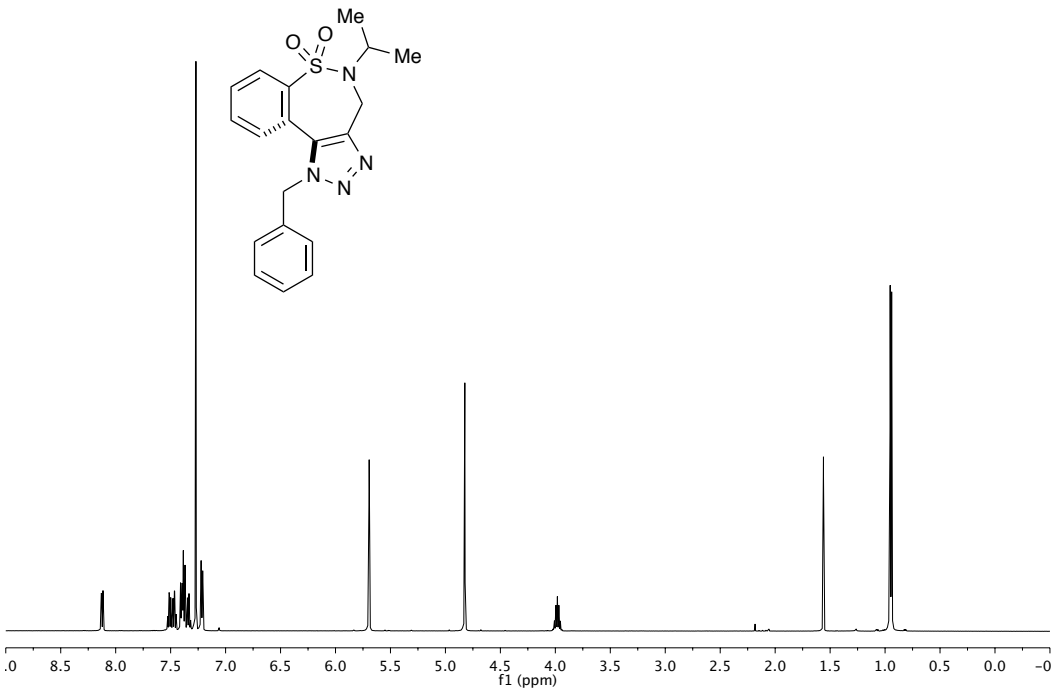


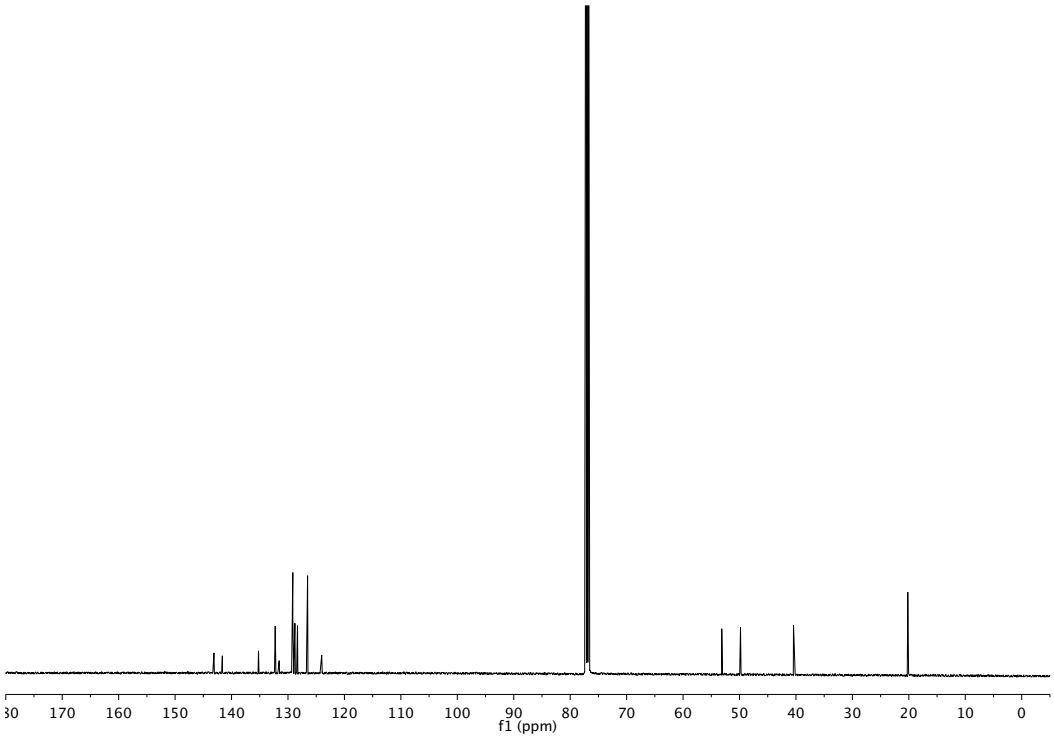
(±)-1-Benzyl-5-ethyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.78)



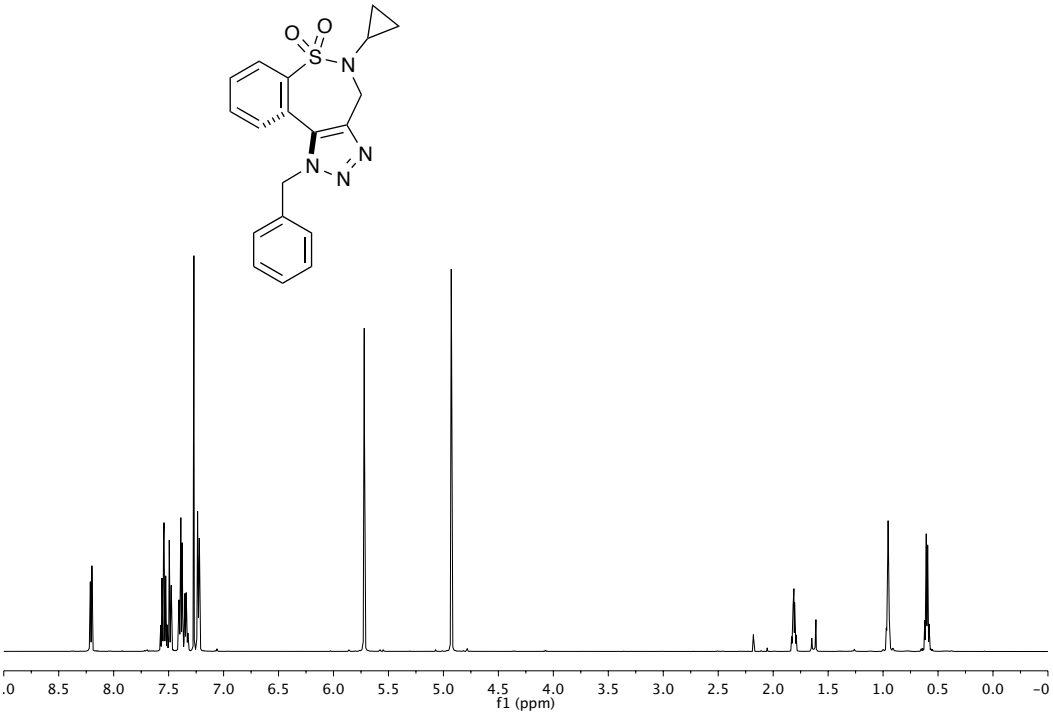


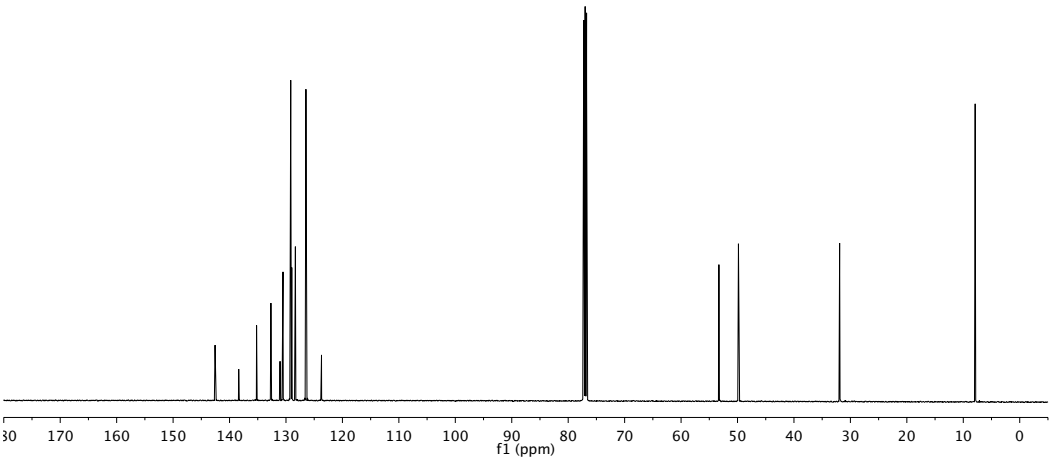
(±)-1-Benzyl-5-isopropyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.79)



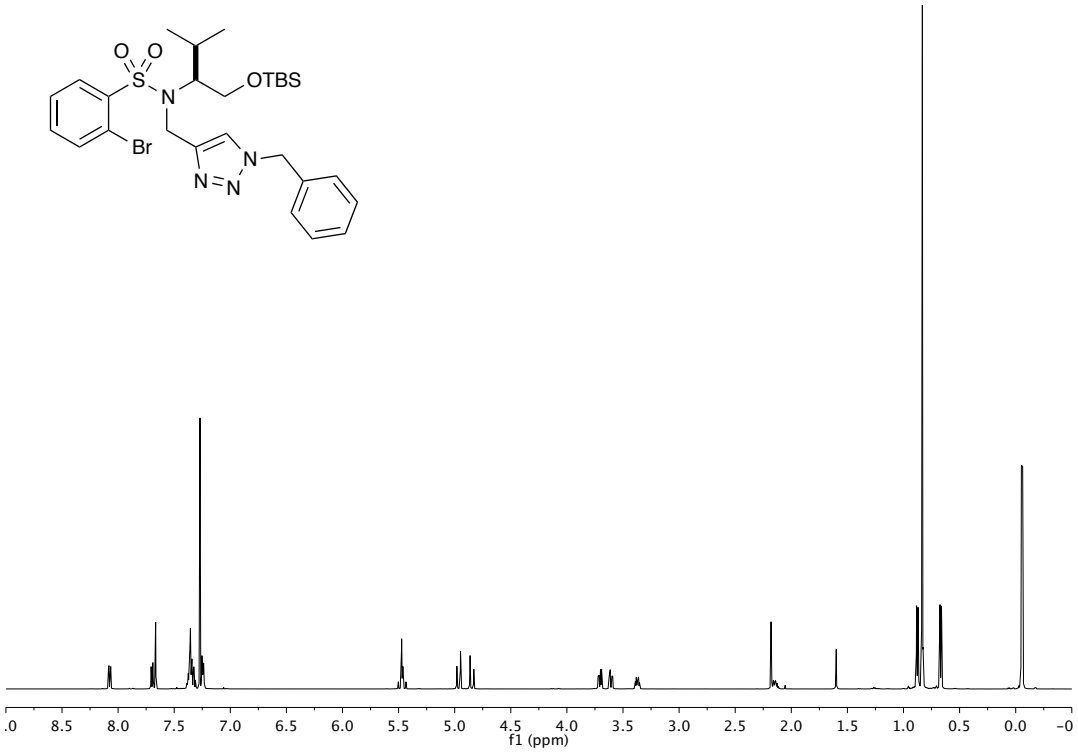


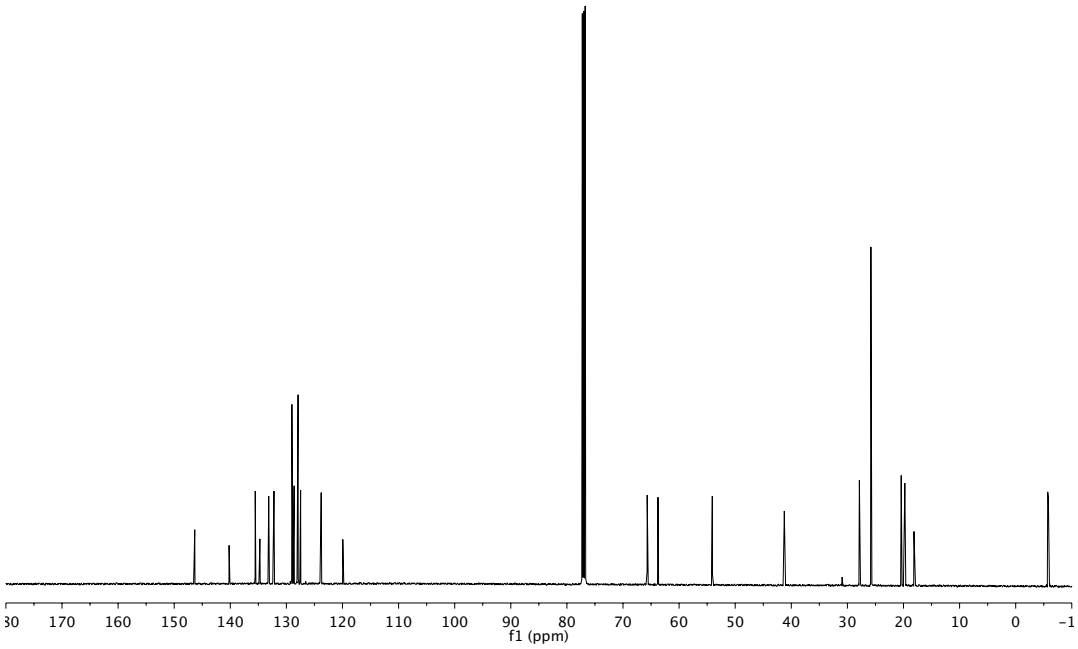
(±)-1-Benzyl-5-cyclopropyl-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.80)



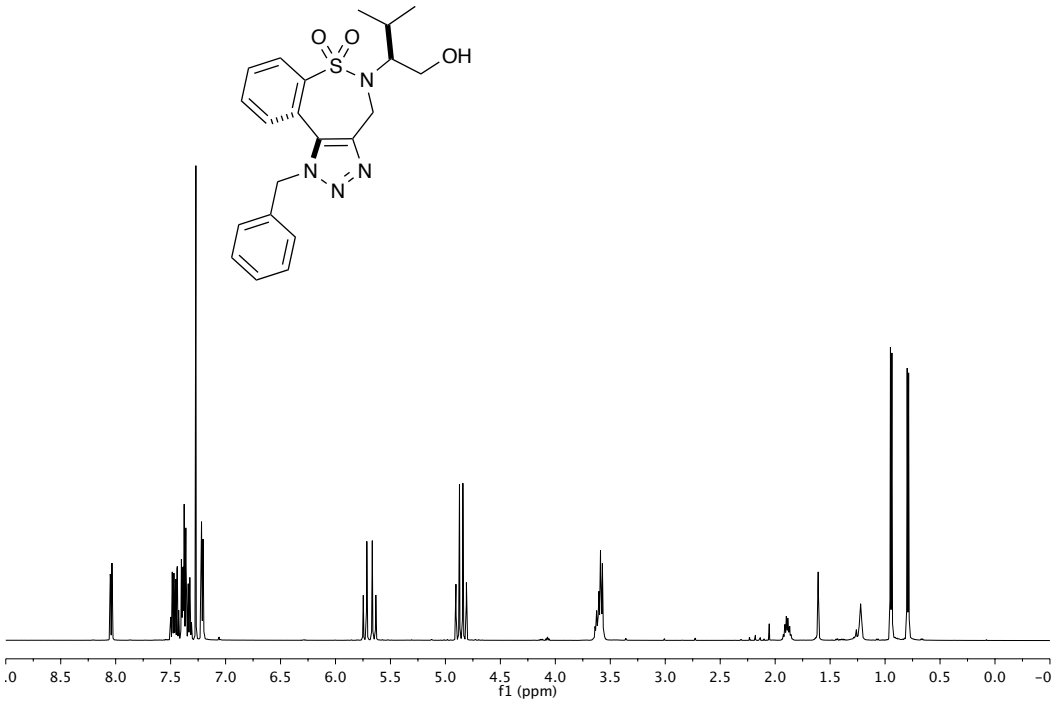


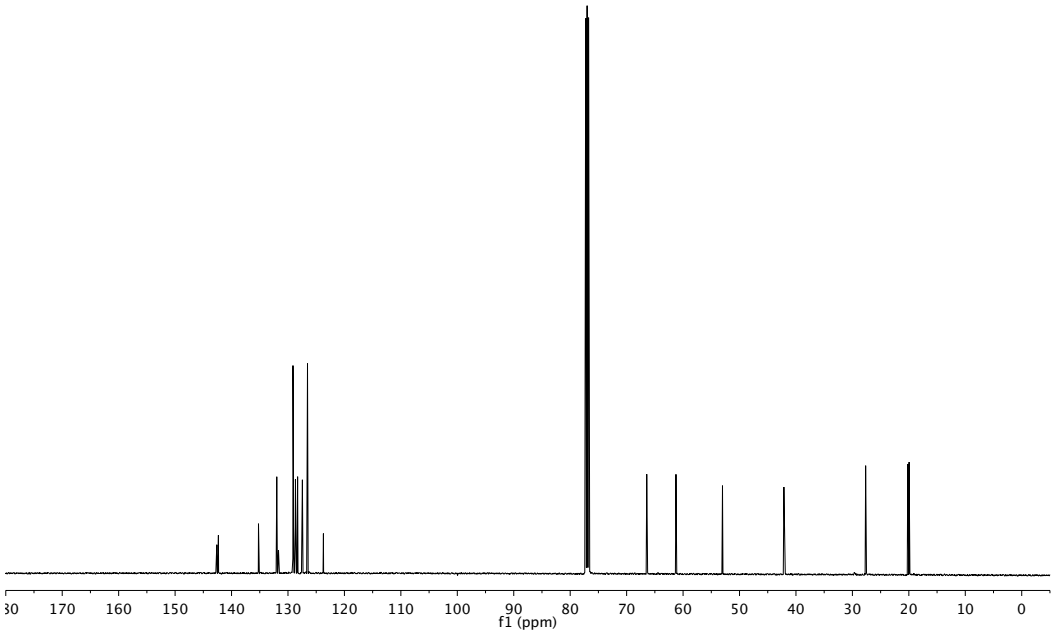
(*S*)-*N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-bromo-*N*-(1-((*tert*-butyldimethylsilyl)oxy)-3-methylbutan-2-yl)benzenesulfonamide (4.81)



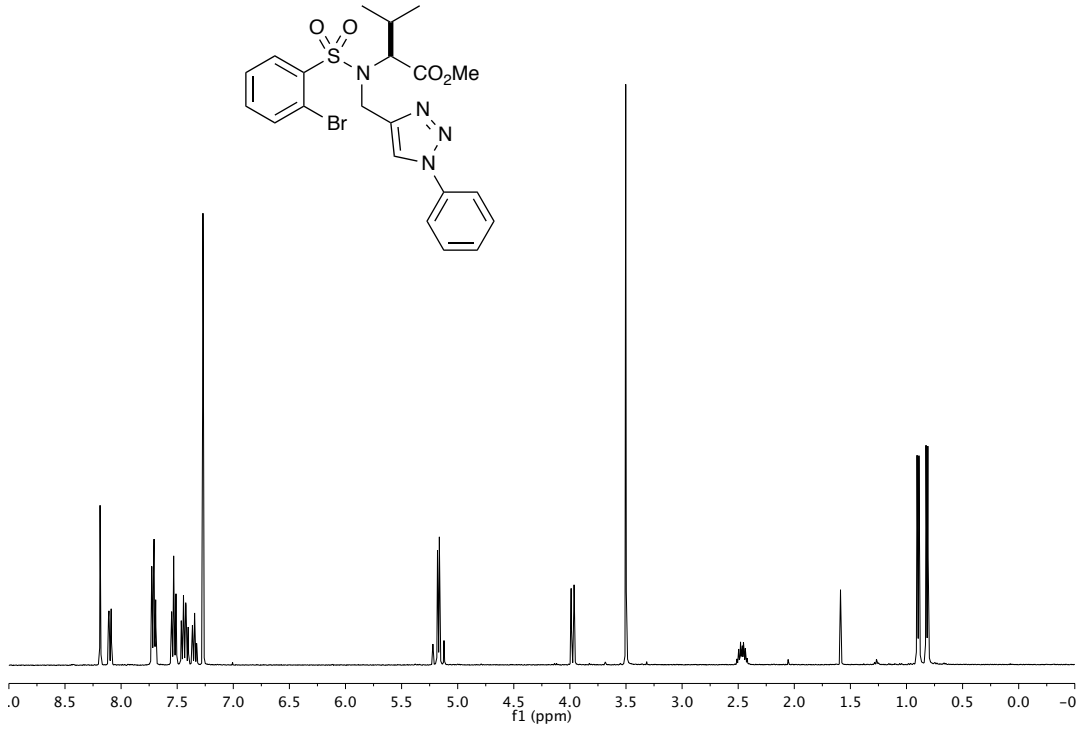


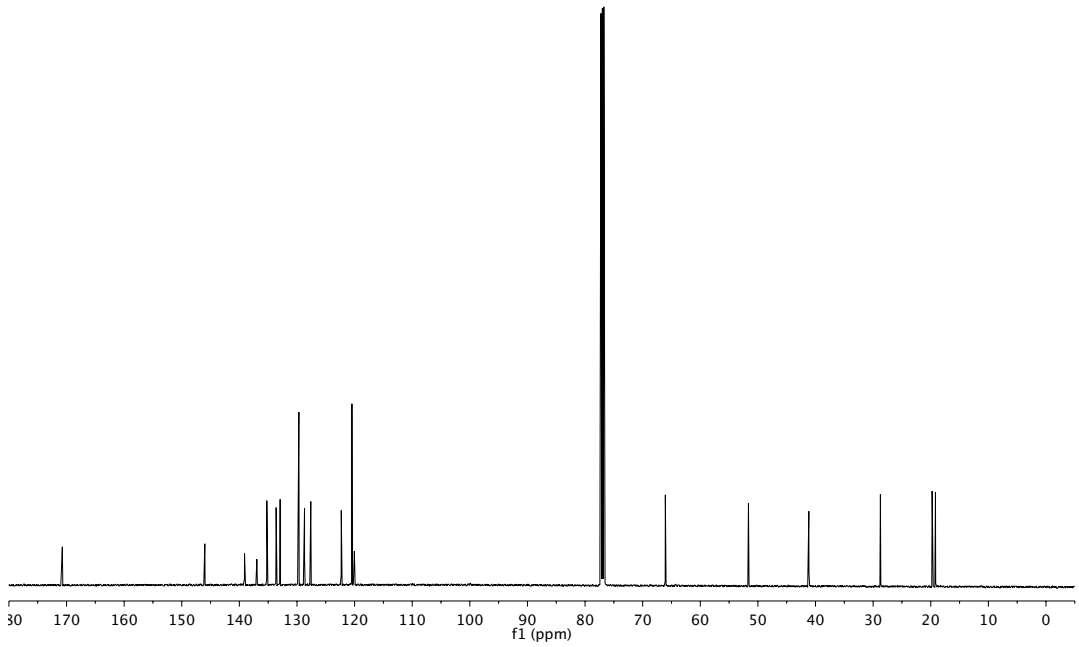
(*S*)-1-Benzyl-5-((*S*$_a$)-1-hydroxy-3-methylbutan-2-yl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.82)



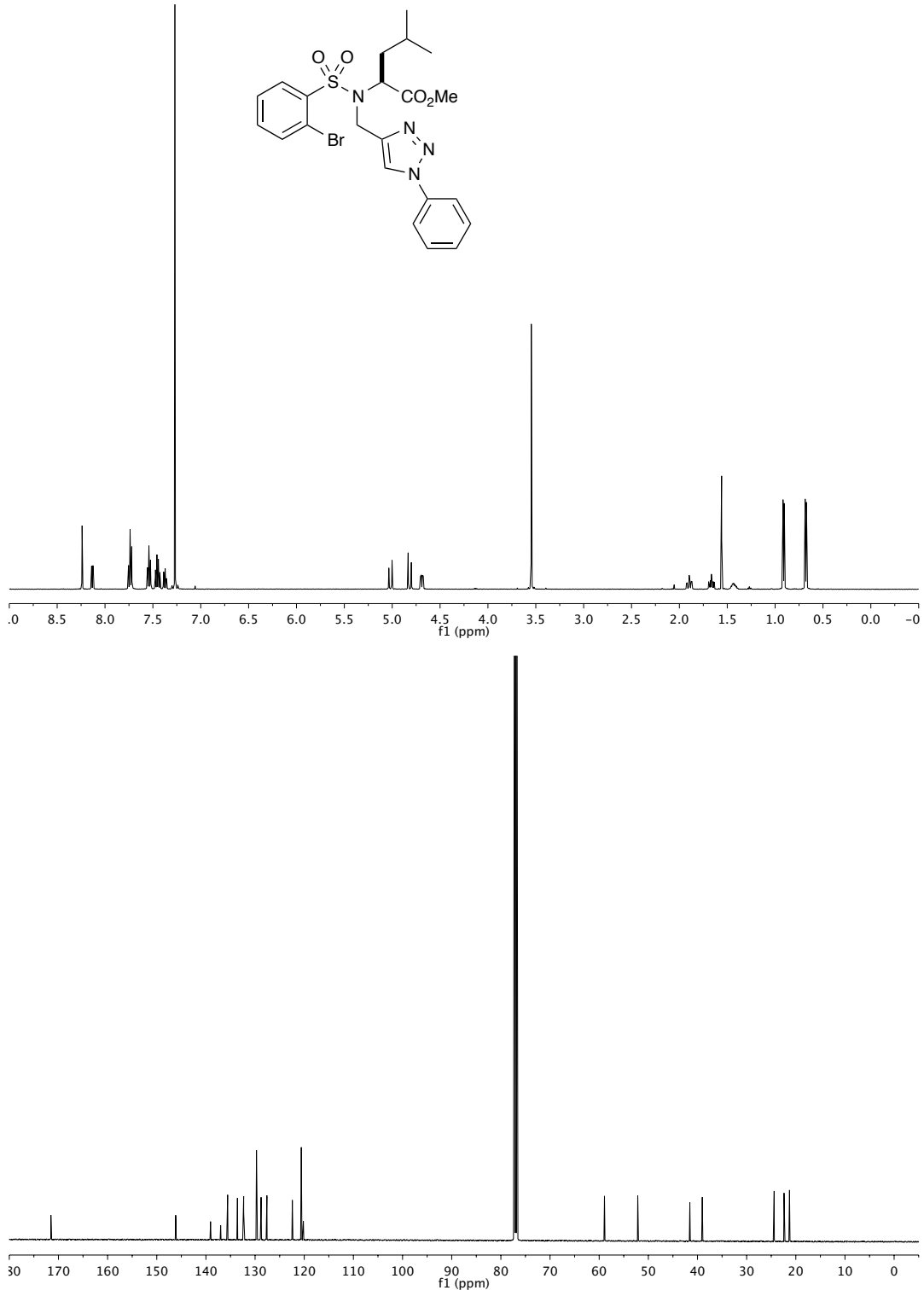


(*S*)-Methyl 2-(2-bromo-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-3-methylbutanoate (4.83)

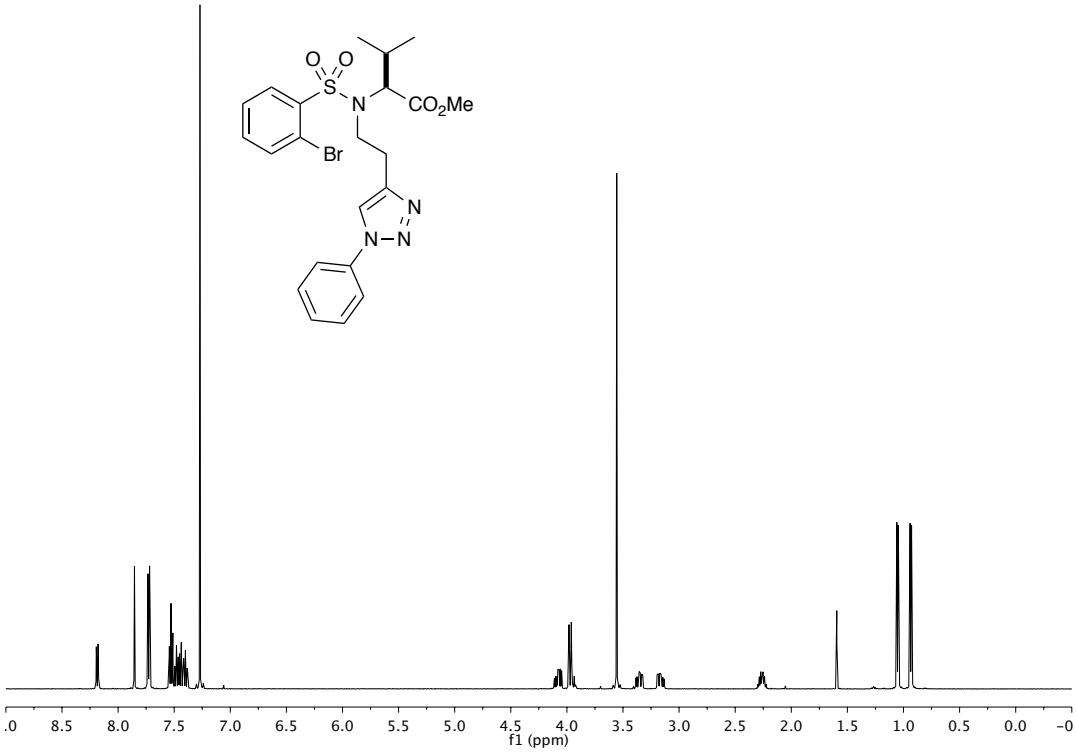


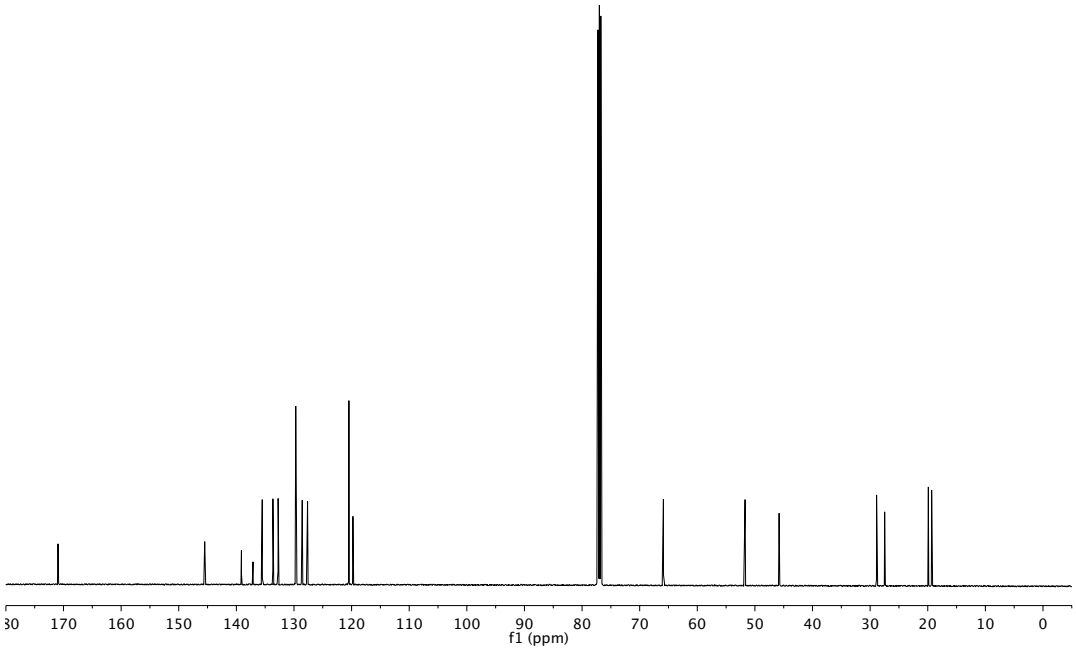


(*S*)-Methyl 2-(2-bromo-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phenylsulfonamido)-4-methylpentanoate (4.84)

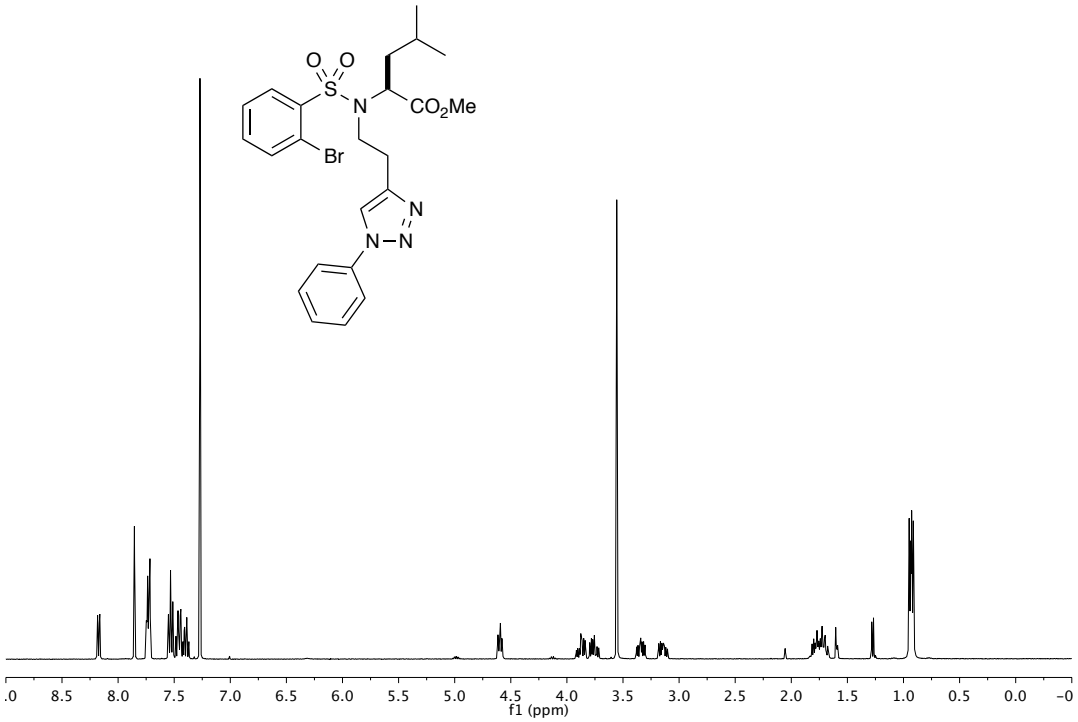


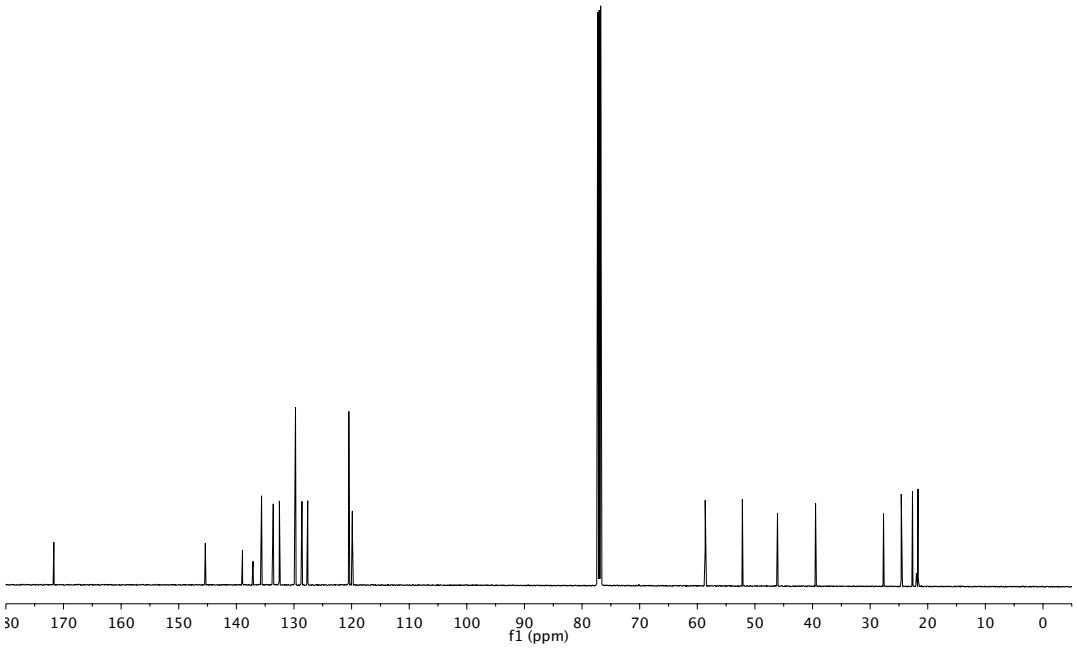
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-3-methylbutanoate (4.85)



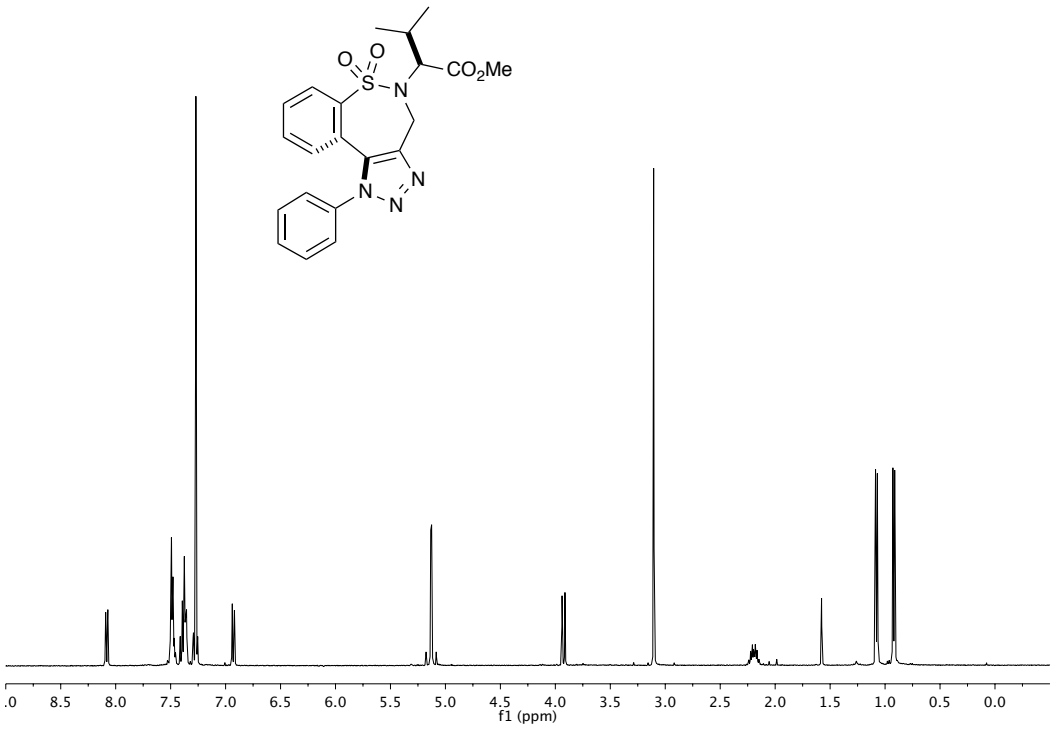


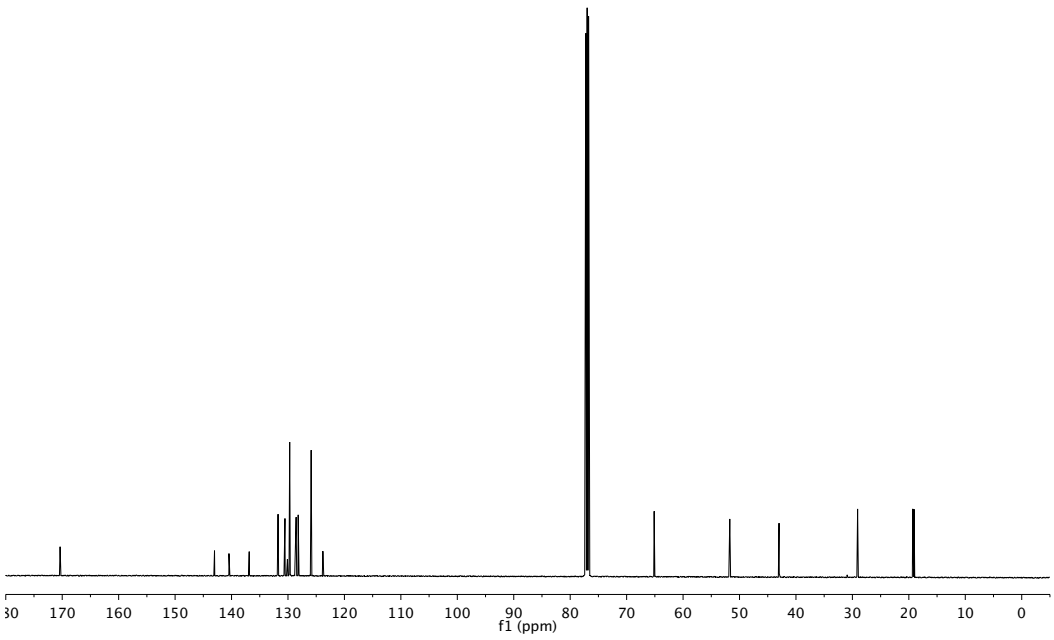
(*S*)-Methyl 2-(2-bromo-*N*-(2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethyl)phenylsulfonamido)-4-methylpentanoate (4.86)



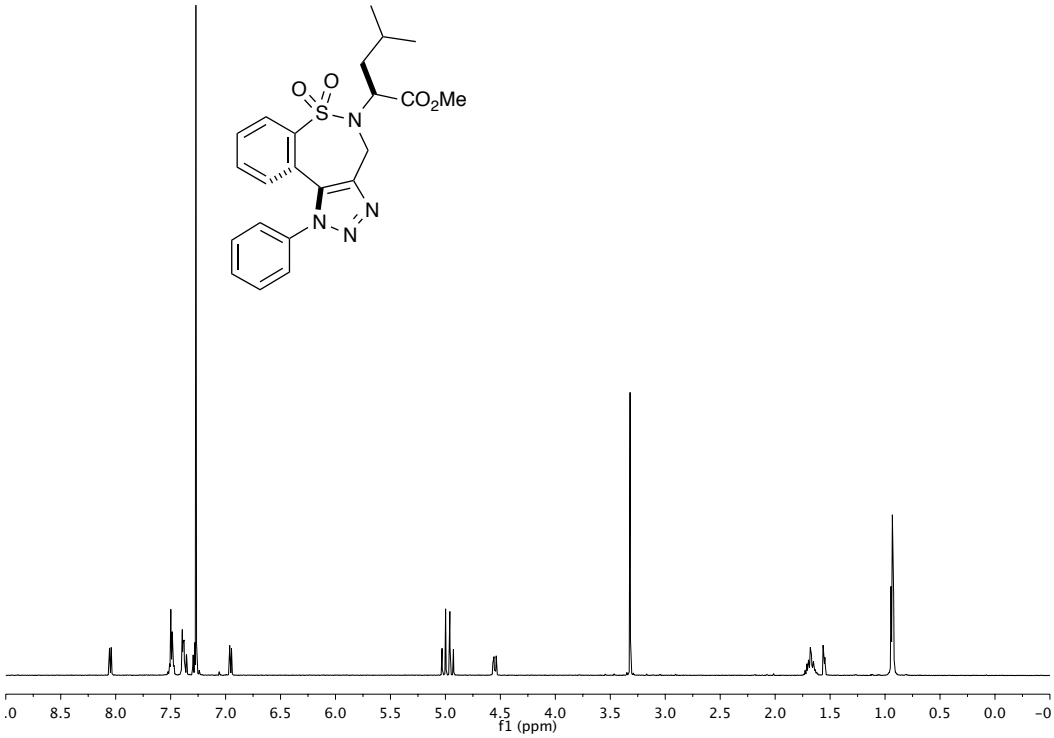


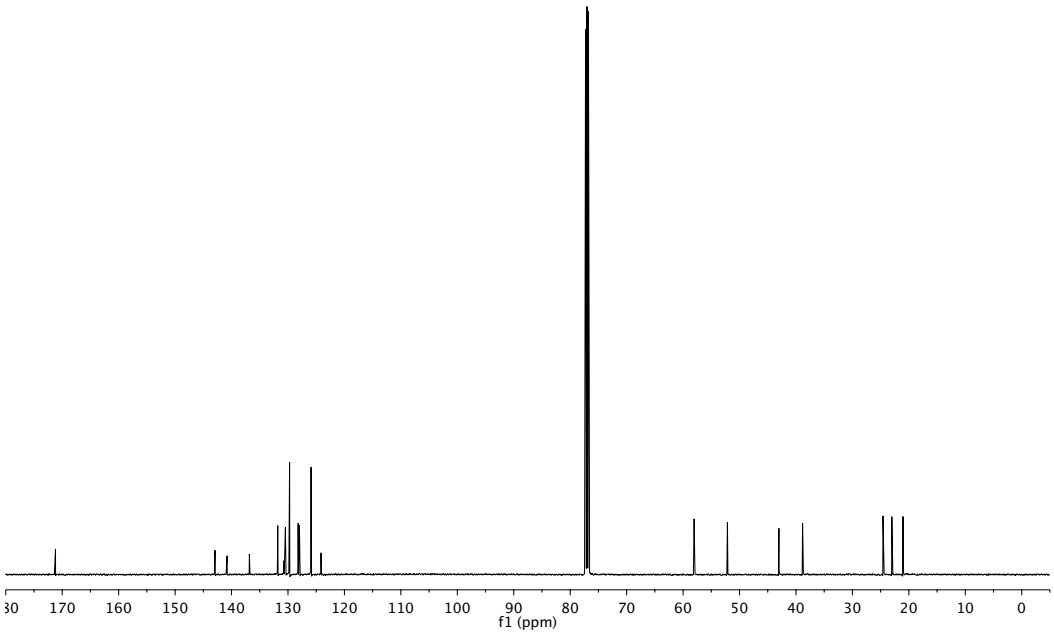
(2*S*)-Methyl 2-(6,6-dioxido-1-phenyl-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.87)



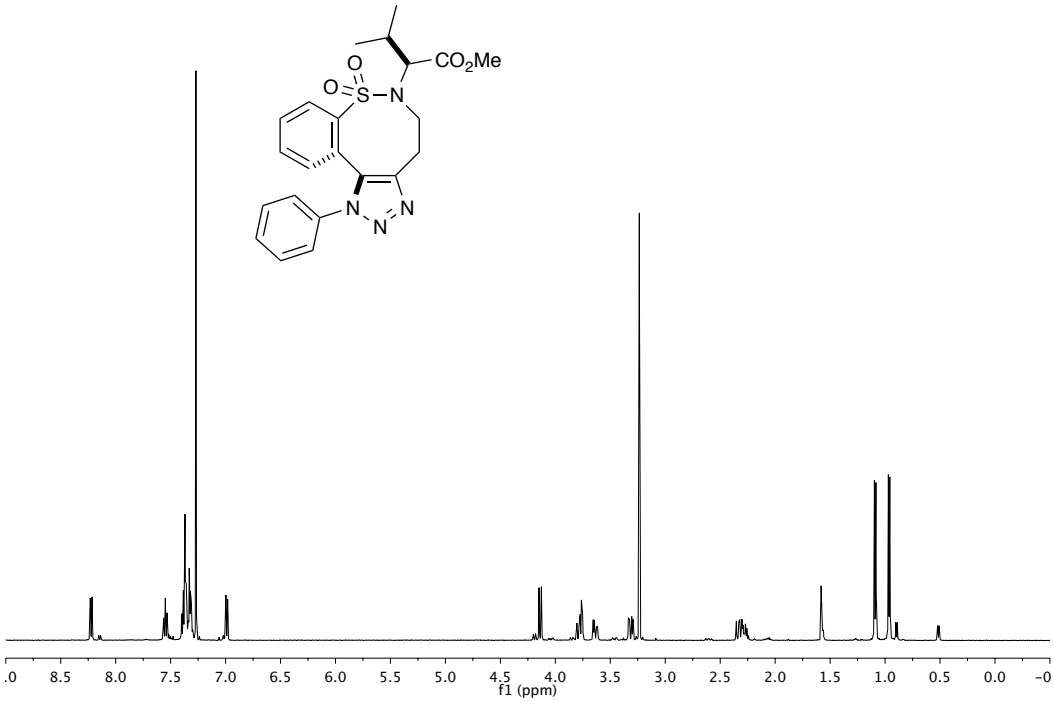


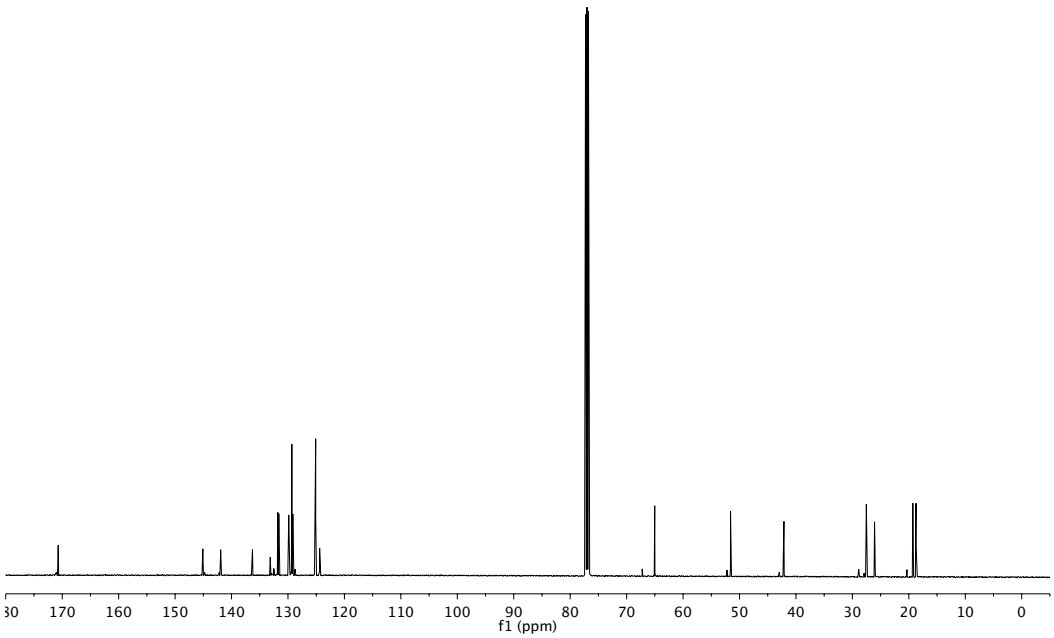
(2*S*)-Methyl 2-(6,6-dioxido-1-phenyl-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.88)



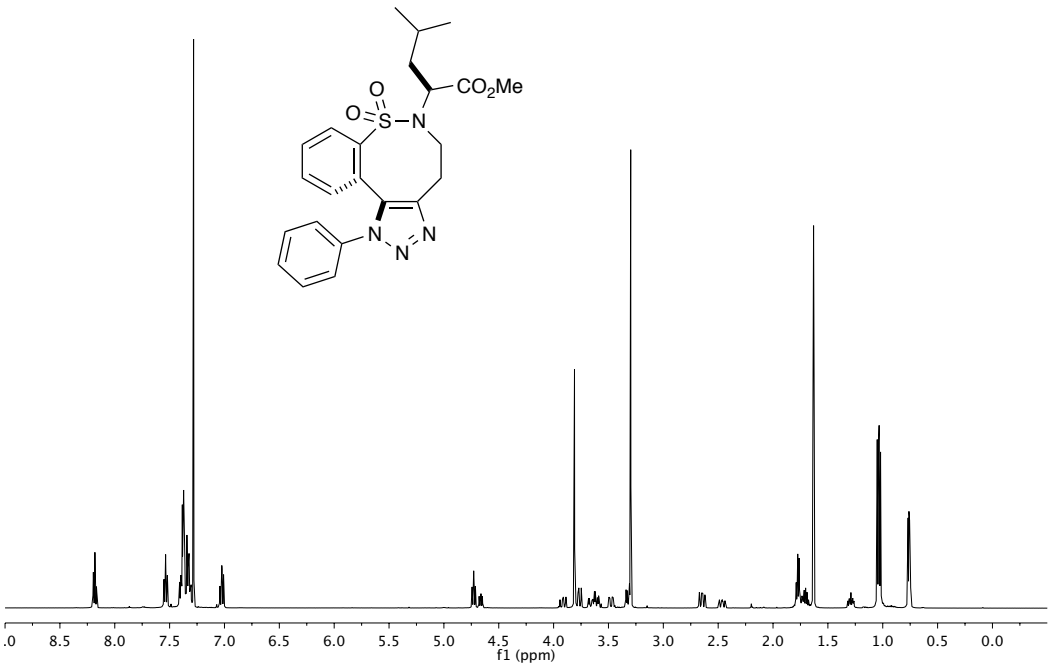


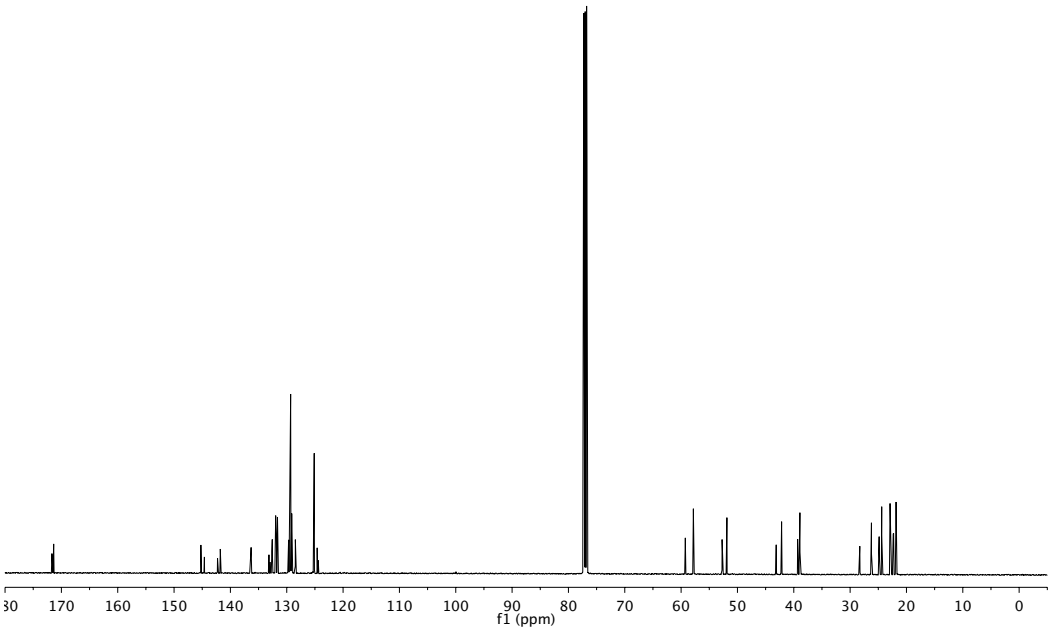
(*S*)-Methyl 2-(7,7-dioxido-1-phenyl-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.89)



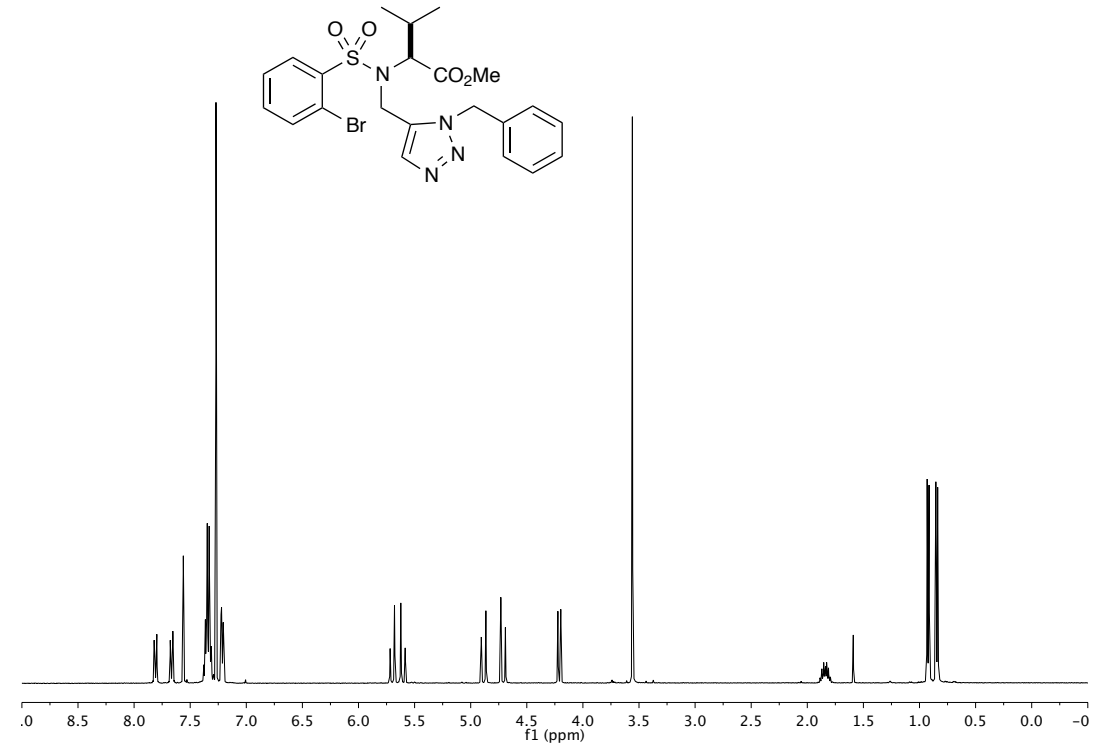


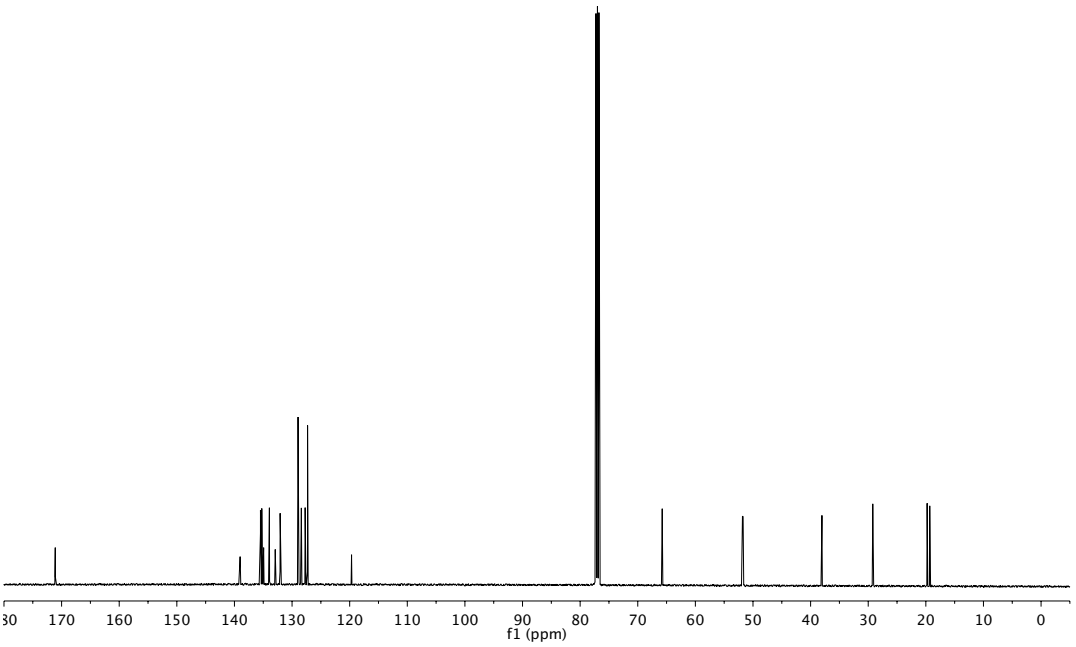
(*S*)-Methyl 2-(7,7-dioxido-1-phenyl-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-4-methylpentanoate (4.90)



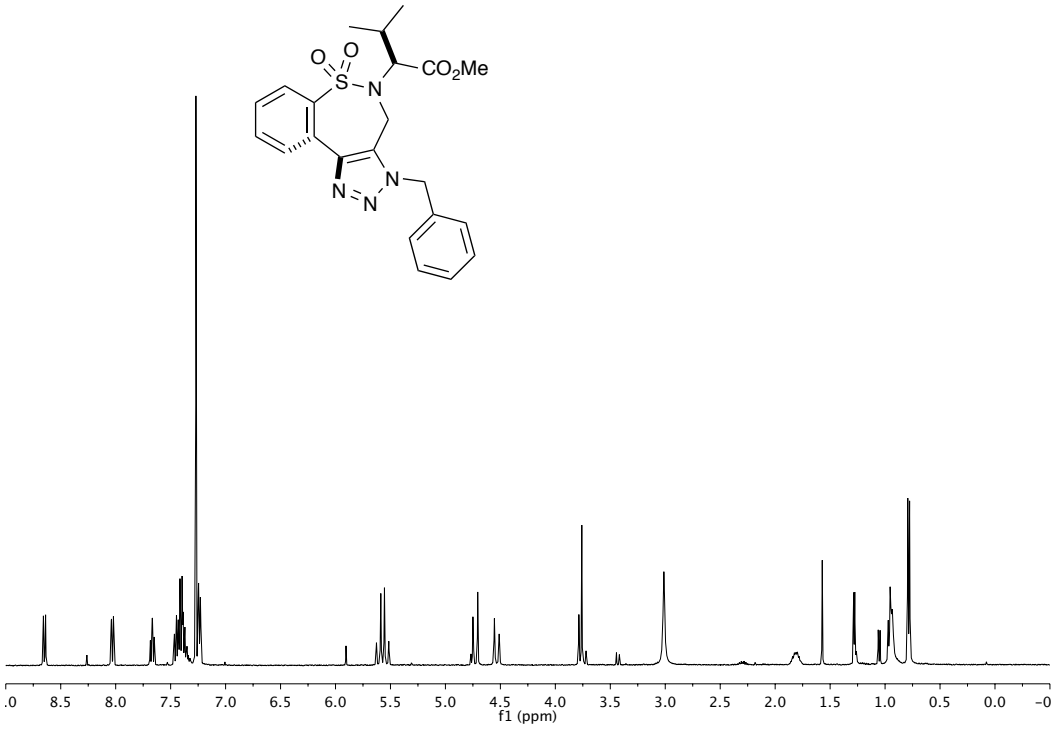


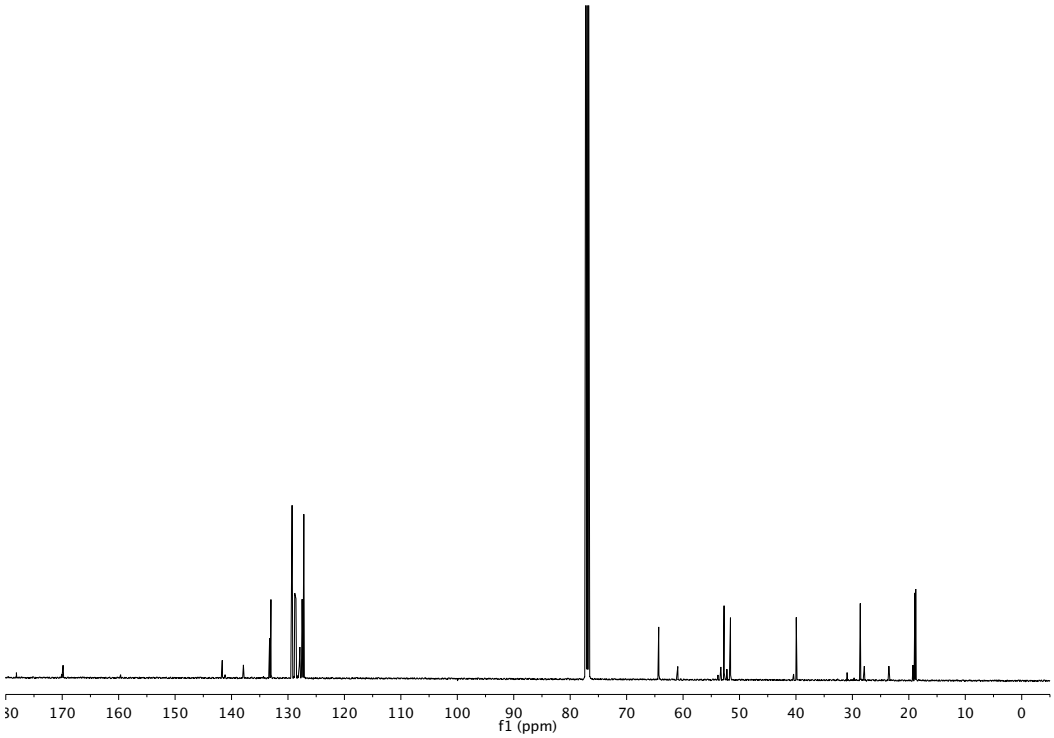
(*S*)-Methyl 2-(*N*-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-2-bromophenylsulfonamido)-3-methylbutanoate (4.91)



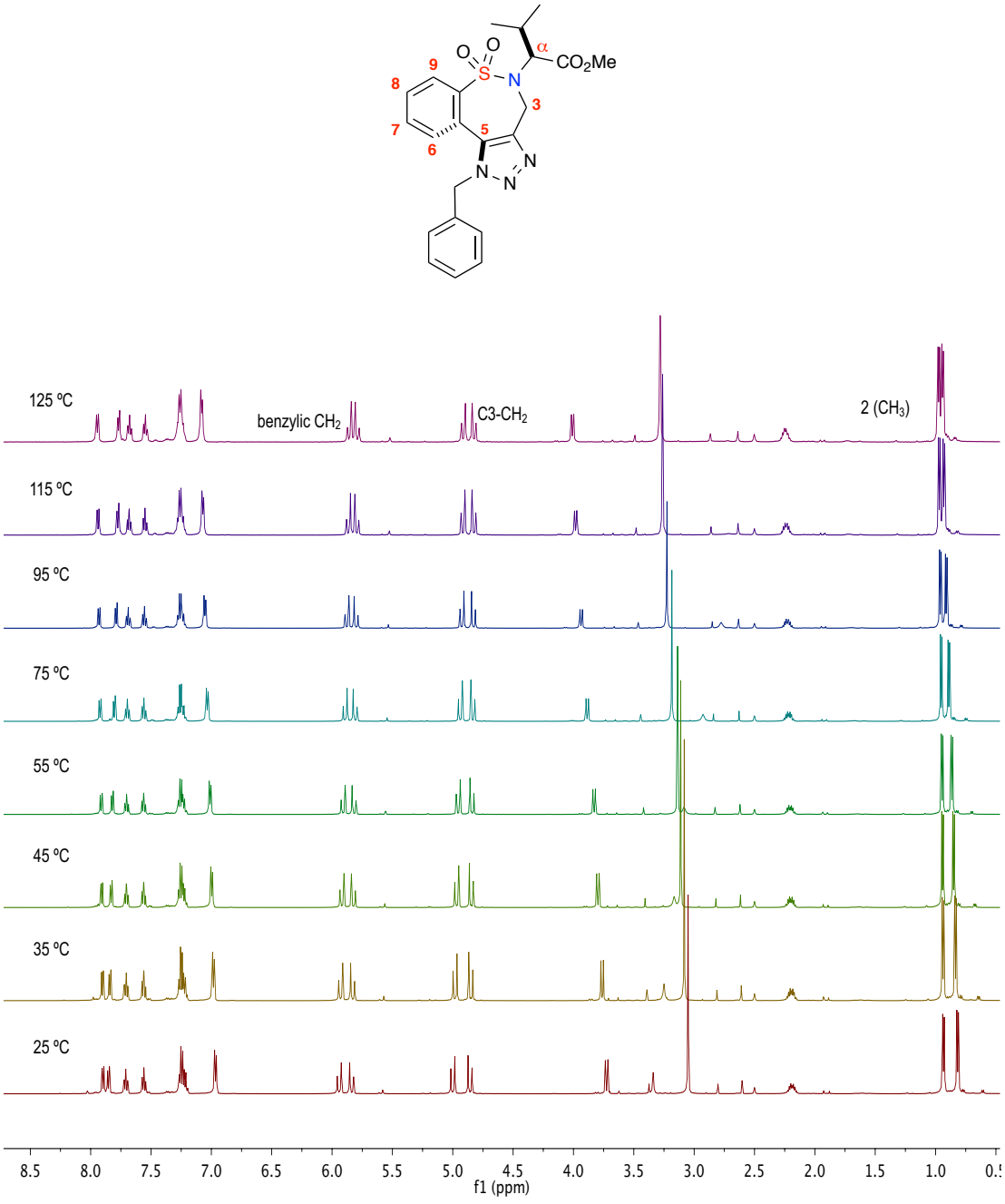


(*S*)-Methyl 2-(3-benzyl-6,6-dioxido-3*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.92)

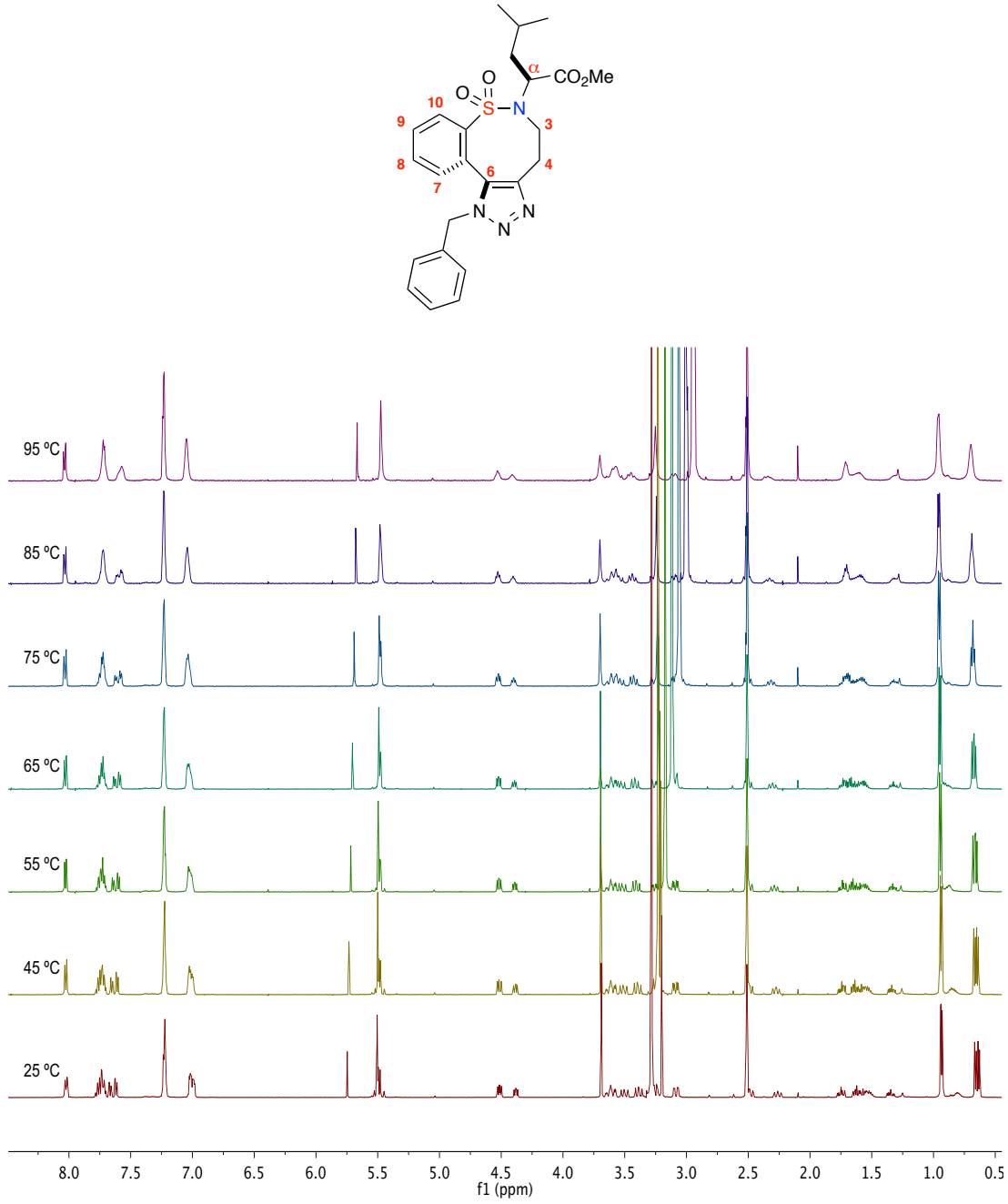




Overlay from high temperature NMR study (**4.40**, DMSO-d_6)



Overlay from high temperature NMR study (**4.70**, DMSO-d_6)



(±)-1-Benzyl-5-(*tert*-butyl)-4,5-dihydro-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepine 6,6-dioxide (4.22)

Table 1. Crystal data and structure refinement for C20H22N4O2S.

Empirical formula	C20 H22 N4 O2 S	
Formula weight	382.48	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.1667(8) Å	α= 94.567(3)°.
	b = 10.7670(11) Å	β= 91.652(3)°.
	c = 10.9430(11) Å	γ = 96.090(3)°.
Volume	953.08(17) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	1.696 mm^{-1}	
F(000)	404	
Crystal size	0.23 x 0.20 x 0.17 mm^3	
Theta range for data collection	4.06 to 69.08°.	
Index ranges	-9<=h<=9, -12<=k<=12, -12<=l<=13	
Reflections collected	13615	
Independent reflections	3319 [R(int) = 0.0342]	
Completeness to theta = 66.00°	95.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.742	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3319 / 0 / 299	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0952	
R indices (all data)	R1 = 0.0370, wR2 = 0.0954	
Largest diff. peak and hole	0.568 and -0.473 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for C20H22N4O2S. U(eq) is defined as one third of the trace of theorthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	7036(1)	8267(1)	8085(1)	22(1)
O(1)	8361(1)	9235(1)	8360(1)	29(1)
O(2)	6906(1)	7215(1)	8821(1)	27(1)
N(1)	7124(2)	7675(1)	6671(1)	23(1)
N(2)	3812(2)	4973(1)	6586(1)	27(1)
N(3)	2355(2)	4918(1)	7083(1)	28(1)
N(4)	2160(2)	6067(1)	7585(1)	24(1)
C(1)	6336(2)	6379(2)	6440(2)	24(1)
C(2)	4573(2)	6161(1)	6799(1)	22(1)
C(3)	3528(2)	6901(1)	7432(1)	21(1)
C(4)	3652(2)	8241(1)	7842(1)	21(1)
C(5)	5172(2)	8970(1)	8167(1)	20(1)
C(6)	5258(2)	10231(2)	8536(1)	23(1)
C(7)	3824(2)	10828(2)	8613(1)	24(1)
C(8)	2323(2)	10135(2)	8291(2)	26(1)
C(9)	2242(2)	8876(2)	7896(1)	25(1)
C(10)	7292(2)	8432(2)	5562(1)	27(1)
C(11)	5637(2)	8334(2)	4850(2)	34(1)
C(12)	8587(2)	7867(2)	4766(2)	38(1)
C(13)	7892(2)	9810(2)	5904(2)	32(1)
C(14)	794(2)	6147(2)	8429(1)	24(1)
C(15)	1404(2)	6417(1)	9750(1)	23(1)
C(16)	2813(2)	5951(2)	10184(2)	32(1)
C(17)	3314(2)	6170(2)	11410(2)	35(1)
C(18)	2403(2)	6843(2)	12219(2)	33(1)
C(19)	996(2)	7306(2)	11796(2)	33(1)
C(20)	501(2)	7103(2)	10564(2)	28(1)

Table 3. Bond lengths [Å] and angles [°] for C20H22N4O2S.

S-O(1)	1.4286(12)
S-O(2)	1.4378(12)
S-N(1)	1.6324(13)
S-C(5)	1.7724(15)
N(1)-C(1)	1.474(2)
N(1)-C(10)	1.516(2)
N(2)-N(3)	1.3194(19)
N(2)-C(2)	1.361(2)
N(3)-N(4)	1.340(2)
N(4)-C(3)	1.3798(19)
N(4)-C(14)	1.4740(19)
C(1)-C(2)	1.503(2)
C(1)-H(1A)	0.965(19)
C(1)-H(1B)	0.96(2)
C(2)-C(3)	1.390(2)
C(3)-C(4)	1.469(2)
C(4)-C(9)	1.400(2)
C(4)-C(5)	1.416(2)
C(5)-C(6)	1.380(2)
C(6)-C(7)	1.395(2)
C(6)-H(6)	0.94(2)
C(7)-C(8)	1.387(2)
C(7)-H(7)	0.95(2)
C(8)-C(9)	1.384(2)
C(8)-H(8)	0.98(2)
C(9)-H(9A)	0.97(2)
C(10)-C(13)	1.526(2)
C(10)-C(11)	1.530(2)
C(10)-C(12)	1.534(2)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800

C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.511(2)
C(14)-H(14A)	0.94(2)
C(14)-H(14B)	0.949(19)
C(15)-C(16)	1.389(2)
C(15)-C(20)	1.390(2)
C(16)-C(17)	1.387(3)
C(16)-H(16)	0.93(2)
C(17)-C(18)	1.382(3)
C(17)-H(17)	0.95(2)
C(18)-C(19)	1.382(3)
C(18)-H(18)	0.95(2)
C(19)-C(20)	1.390(2)
C(19)-H(19)	0.93(2)
C(20)-H(20)	0.95(2)

O(1)-S-O(2)	118.38(7)
O(1)-S-N(1)	109.92(7)
O(2)-S-N(1)	105.74(7)
O(1)-S-C(5)	107.57(7)
O(2)-S-C(5)	108.38(7)
N(1)-S-C(5)	106.23(7)
C(1)-N(1)-C(10)	116.08(12)
C(1)-N(1)-S	114.26(10)
C(10)-N(1)-S	125.02(11)
N(3)-N(2)-C(2)	108.82(13)
N(2)-N(3)-N(4)	107.81(12)
N(3)-N(4)-C(3)	111.15(12)
N(3)-N(4)-C(14)	116.03(12)
C(3)-N(4)-C(14)	130.79(14)
N(1)-C(1)-C(2)	115.73(13)
N(1)-C(1)-H(1A)	109.5(11)
C(2)-C(1)-H(1A)	107.8(10)
N(1)-C(1)-H(1B)	109.9(11)
C(2)-C(1)-H(1B)	108.8(11)
H(1A)-C(1)-H(1B)	104.5(15)
N(2)-C(2)-C(3)	109.14(13)

N(2)-C(2)-C(1)	116.93(13)
C(3)-C(2)-C(1)	133.61(14)
N(4)-C(3)-C(2)	103.05(13)
N(4)-C(3)-C(4)	123.75(13)
C(2)-C(3)-C(4)	133.16(13)
C(9)-C(4)-C(5)	116.32(14)
C(9)-C(4)-C(3)	120.65(13)
C(5)-C(4)-C(3)	123.01(13)
C(6)-C(5)-C(4)	121.93(14)
C(6)-C(5)-S	118.17(11)
C(4)-C(5)-S	119.89(12)
C(5)-C(6)-C(7)	120.31(15)
C(5)-C(6)-H(6)	119.1(12)
C(7)-C(6)-H(6)	120.6(12)
C(8)-C(7)-C(6)	118.77(16)
C(8)-C(7)-H(7)	122.0(11)
C(6)-C(7)-H(7)	119.3(11)
C(9)-C(8)-C(7)	120.83(15)
C(9)-C(8)-H(8)	119.4(12)
C(7)-C(8)-H(8)	119.7(12)
C(8)-C(9)-C(4)	121.80(15)
C(8)-C(9)-H(9A)	119.9(12)
C(4)-C(9)-H(9A)	118.3(12)
N(1)-C(10)-C(13)	112.69(13)
N(1)-C(10)-C(11)	109.89(12)
C(13)-C(10)-C(11)	109.30(15)
N(1)-C(10)-C(12)	106.56(14)
C(13)-C(10)-C(12)	107.97(13)
C(11)-C(10)-C(12)	110.37(14)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5

C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(10)-C(13)-H(13A)	109.5
C(10)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
N(4)-C(14)-C(15)	112.00(12)
N(4)-C(14)-H(14A)	104.2(11)
C(15)-C(14)-H(14A)	110.2(11)
N(4)-C(14)-H(14B)	109.1(11)
C(15)-C(14)-H(14B)	112.0(11)
H(14A)-C(14)-H(14B)	109.1(16)
C(16)-C(15)-C(20)	119.04(15)
C(16)-C(15)-C(14)	121.53(15)
C(20)-C(15)-C(14)	119.38(14)
C(17)-C(16)-C(15)	120.49(17)
C(17)-C(16)-H(16)	120.1(14)
C(15)-C(16)-H(16)	119.4(14)
C(18)-C(17)-C(16)	120.24(17)
C(18)-C(17)-H(17)	119.3(13)
C(16)-C(17)-H(17)	120.4(13)
C(19)-C(18)-C(17)	119.69(16)
C(19)-C(18)-H(18)	119.7(14)
C(17)-C(18)-H(18)	120.6(14)
C(18)-C(19)-C(20)	120.28(17)
C(18)-C(19)-H(19)	119.7(14)
C(20)-C(19)-H(19)	120.0(14)
C(15)-C(20)-C(19)	120.26(16)
C(15)-C(20)-H(20)	118.7(13)
C(19)-C(20)-H(20)	121.0(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C20H22N4O2S. The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	17(1)	26(1)	24(1)	0(1)	3(1)	1(1)
O(1)	18(1)	34(1)	32(1)	-4(1)	2(1)	-2(1)
O(2)	26(1)	31(1)	26(1)	5(1)	2(1)	6(1)
N(1)	21(1)	23(1)	25(1)	1(1)	7(1)	-2(1)
N(2)	26(1)	25(1)	28(1)	1(1)	8(1)	-2(1)
N(3)	28(1)	24(1)	30(1)	-1(1)	9(1)	-4(1)
N(4)	21(1)	22(1)	25(1)	0(1)	6(1)	-4(1)
C(1)	23(1)	22(1)	27(1)	1(1)	8(1)	0(1)
C(2)	23(1)	23(1)	21(1)	2(1)	4(1)	-1(1)
C(3)	18(1)	23(1)	22(1)	3(1)	3(1)	-2(1)
C(4)	20(1)	23(1)	20(1)	4(1)	5(1)	0(1)
C(5)	18(1)	24(1)	18(1)	3(1)	5(1)	0(1)
C(6)	22(1)	25(1)	21(1)	2(1)	4(1)	-2(1)
C(7)	28(1)	21(1)	24(1)	2(1)	7(1)	2(1)
C(8)	23(1)	27(1)	30(1)	6(1)	7(1)	5(1)
C(9)	19(1)	27(1)	28(1)	4(1)	4(1)	0(1)
C(10)	29(1)	28(1)	25(1)	3(1)	9(1)	-6(1)
C(11)	40(1)	33(1)	27(1)	8(1)	1(1)	-6(1)
C(12)	41(1)	32(1)	38(1)	-5(1)	22(1)	-10(1)
C(13)	35(1)	27(1)	31(1)	2(1)	12(1)	-6(1)
C(14)	19(1)	26(1)	28(1)	2(1)	8(1)	-3(1)
C(15)	20(1)	20(1)	28(1)	5(1)	6(1)	-4(1)
C(16)	28(1)	35(1)	34(1)	8(1)	9(1)	6(1)
C(17)	26(1)	42(1)	39(1)	16(1)	0(1)	2(1)
C(18)	34(1)	33(1)	29(1)	7(1)	-2(1)	-10(1)
C(19)	39(1)	30(1)	29(1)	-2(1)	5(1)	2(1)
C(20)	26(1)	28(1)	30(1)	2(1)	3(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C20H22N4O2S.

	x	y	z	U(eq)
H(1A)	6960(20)	5824(17)	6870(16)	21(4)
H(1B)	6400(20)	6100(18)	5588(18)	25(4)
H(6)	6290(20)	10683(19)	8722(17)	29(5)
H(7)	3900(20)	11692(19)	8875(17)	23(4)
H(8)	1300(30)	10550(20)	8323(19)	35(5)
H(9A)	1190(30)	8419(19)	7616(18)	32(5)
H(11A)	5285	7454	4581	51
H(11B)	5756	8821	4133	51
H(11C)	4811	8664	5381	51
H(12A)	9630	7915	5241	57
H(12B)	8750	8338	4041	57
H(12C)	8207	6989	4508	57
H(13A)	7101	10184	6438	47
H(13B)	7991	10254	5158	47
H(13C)	8969	9877	6337	47
H(14A)	190(20)	5347(19)	8315(17)	25(4)
H(14B)	120(20)	6757(18)	8180(16)	22(4)
H(16)	3410(30)	5480(20)	9650(20)	40(6)
H(17)	4280(30)	5860(20)	11700(20)	40(6)
H(18)	2740(30)	7000(20)	13060(20)	45(6)
H(19)	400(30)	7780(20)	12330(20)	43(6)
H(20)	-460(30)	7430(20)	10260(19)	37(5)

Table 6. Torsion angles [°] for C20H22N4O2S.

O(1)-S-N(1)-C(1)	154.96(11)
O(2)-S-N(1)-C(1)	26.10(12)
C(5)-S-N(1)-C(1)	-88.94(12)
O(1)-S-N(1)-C(10)	-50.27(14)
O(2)-S-N(1)-C(10)	-179.13(12)
C(5)-S-N(1)-C(10)	65.83(13)
C(2)-N(2)-N(3)-N(4)	1.51(17)
N(2)-N(3)-N(4)-C(3)	-0.77(17)
N(2)-N(3)-N(4)-C(14)	-166.36(13)
C(10)-N(1)-C(1)-C(2)	-102.63(15)
S-N(1)-C(1)-C(2)	54.50(16)
N(3)-N(2)-C(2)-C(3)	-1.70(17)
N(3)-N(2)-C(2)-C(1)	172.69(13)
N(1)-C(1)-C(2)-N(2)	179.51(13)
N(1)-C(1)-C(2)-C(3)	-7.8(3)
N(3)-N(4)-C(3)-C(2)	-0.25(16)
C(14)-N(4)-C(3)-C(2)	162.56(15)
N(3)-N(4)-C(3)-C(4)	177.49(13)
C(14)-N(4)-C(3)-C(4)	-19.7(2)
N(2)-C(2)-C(3)-N(4)	1.16(16)
C(1)-C(2)-C(3)-N(4)	-171.92(16)
N(2)-C(2)-C(3)-C(4)	-176.27(15)
C(1)-C(2)-C(3)-C(4)	10.7(3)
N(4)-C(3)-C(4)-C(9)	-29.4(2)
C(2)-C(3)-C(4)-C(9)	147.56(17)
N(4)-C(3)-C(4)-C(5)	152.41(14)
C(2)-C(3)-C(4)-C(5)	-30.6(2)
C(9)-C(4)-C(5)-C(6)	1.0(2)
C(3)-C(4)-C(5)-C(6)	179.27(13)
C(9)-C(4)-C(5)-S	-178.11(11)
C(3)-C(4)-C(5)-S	0.13(19)
O(1)-S-C(5)-C(6)	-4.07(14)
O(2)-S-C(5)-C(6)	125.02(12)
N(1)-S-C(5)-C(6)	-121.75(12)
O(1)-S-C(5)-C(4)	175.09(11)
O(2)-S-C(5)-C(4)	-55.82(13)

N(1)-S-C(5)-C(4)	57.42(13)
C(4)-C(5)-C(6)-C(7)	0.7(2)
S-C(5)-C(6)-C(7)	179.87(11)
C(5)-C(6)-C(7)-C(8)	-1.1(2)
C(6)-C(7)-C(8)-C(9)	-0.3(2)
C(7)-C(8)-C(9)-C(4)	2.1(2)
C(5)-C(4)-C(9)-C(8)	-2.4(2)
C(3)-C(4)-C(9)-C(8)	179.27(14)
C(1)-N(1)-C(10)-C(13)	171.86(13)
S-N(1)-C(10)-C(13)	17.50(19)
C(1)-N(1)-C(10)-C(11)	49.70(18)
S-N(1)-C(10)-C(11)	-104.66(15)
C(1)-N(1)-C(10)-C(12)	-69.89(16)
S-N(1)-C(10)-C(12)	135.74(12)
N(3)-N(4)-C(14)-C(15)	108.12(15)
C(3)-N(4)-C(14)-C(15)	-54.0(2)
N(4)-C(14)-C(15)-C(16)	-34.0(2)
N(4)-C(14)-C(15)-C(20)	148.72(14)
C(20)-C(15)-C(16)-C(17)	-0.1(2)
C(14)-C(15)-C(16)-C(17)	-177.45(15)
C(15)-C(16)-C(17)-C(18)	0.7(3)
C(16)-C(17)-C(18)-C(19)	-0.5(3)
C(17)-C(18)-C(19)-C(20)	-0.3(3)
C(16)-C(15)-C(20)-C(19)	-0.7(2)
C(14)-C(15)-C(20)-C(19)	176.69(15)
C(18)-C(19)-C(20)-C(15)	0.9(3)

Symmetry transformations used to generate equivalent atoms:

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.40)

Table 1. Crystal data and structure refinement for C22H24N4O4S.

Empirical formula	C22 H24 N4 O4 S	
Formula weight	440.51	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.3353(5) Å	α= 90°.
	b = 15.2338(9) Å	β= 113.4630(10)°.
	c = 9.2265(5) Å	γ = 90°.
Volume	1074.70(11) Å^3	
Z	2	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	1.651 mm^{-1}	
F(000)	464	
Crystal size	0.18 x 0.14 x 0.11 mm^3	
Theta range for data collection	5.23 to 69.31°.	
Index ranges	-9<=h<=9, -17<=k<=14, -11<=l<=10	
Reflections collected	8997	
Independent reflections	3039 [R(int) = 0.0258]	
Completeness to theta = 66.00°	98.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.910	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3039 / 1 / 377	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0627	
R indices (all data)	R1 = 0.0256, wR2 = 0.0627	
Absolute structure parameter	0.094(13)	
Extinction coefficient	0.0077(9)	
Largest diff. peak and hole	0.223 and -0.225 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C22H24N4O4S. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	-2521(1)	3681(1)	2601(1)	18(1)
O(1)	-2899(2)	4448(1)	1622(2)	23(1)
O(2)	-3314(2)	3586(1)	3718(1)	22(1)
O(3)	-727(2)	1210(1)	4085(2)	33(1)
O(4)	-422(2)	1531(1)	1840(2)	38(1)
N(1)	-3089(2)	2832(1)	1425(2)	20(1)
N(2)	-1305(2)	3637(1)	-1470(2)	27(1)
N(3)	177(2)	4036(1)	-1205(2)	28(1)
N(4)	1128(2)	4027(1)	369(2)	23(1)
C(1)	-2917(3)	2906(2)	-104(2)	24(1)
C(2)	-1328(2)	3373(1)	-73(2)	22(1)
C(3)	229(2)	3619(1)	1135(2)	20(1)
C(4)	892(2)	3543(1)	2870(2)	20(1)
C(5)	-233(2)	3583(1)	3673(2)	18(1)
C(6)	388(2)	3522(1)	5305(2)	20(1)
C(7)	2167(3)	3430(1)	6186(2)	25(1)
C(8)	3307(2)	3384(1)	5425(2)	27(1)
C(9)	2666(3)	3425(1)	3789(2)	25(1)
C(10)	-3063(2)	1967(1)	2138(2)	21(1)
C(11)	-4521(3)	1351(2)	1055(2)	27(1)
C(12)	-4522(3)	494(2)	1922(3)	33(1)
C(13)	-6294(3)	1790(2)	496(3)	43(1)
C(14)	2745(3)	4538(2)	956(2)	27(1)
C(15)	2675(3)	5323(1)	1926(2)	22(1)
C(16)	4204(3)	5613(2)	3132(2)	30(1)
C(17)	4193(3)	6369(2)	3956(2)	30(1)
C(18)	2673(3)	6842(1)	3601(2)	27(1)
C(19)	1135(3)	6543(2)	2425(2)	29(1)
C(20)	1143(3)	5791(2)	1589(2)	26(1)
C(21)	-1257(3)	1541(1)	2640(2)	25(1)
C(22)	978(3)	797(2)	4684(3)	45(1)

Table 3. Bond lengths [Å] and angles [°] for C22H24N4O4S.

S-O(1)	1.4329(15)
S-O(2)	1.4367(12)
S-N(1)	1.6322(17)
S-C(5)	1.7708(16)
O(3)-C(21)	1.326(2)
O(3)-C(22)	1.448(3)
O(4)-C(21)	1.199(3)
N(1)-C(10)	1.469(3)
N(1)-C(1)	1.477(2)
N(2)-N(3)	1.309(2)
N(2)-C(2)	1.358(2)
N(3)-N(4)	1.349(2)
N(4)-C(3)	1.367(2)
N(4)-C(14)	1.461(3)
C(1)-C(2)	1.494(3)
C(1)-H(1A)	0.99(3)
C(1)-H(1B)	0.94(3)
C(2)-C(3)	1.384(3)
C(3)-C(4)	1.476(2)
C(4)-C(9)	1.392(3)
C(4)-C(5)	1.409(2)
C(5)-C(6)	1.387(2)
C(6)-C(7)	1.385(3)
C(6)-H(6)	0.93(2)
C(7)-C(8)	1.391(3)
C(7)-H(7)	0.98(2)
C(8)-C(9)	1.387(3)
C(8)-H(8)	1.03(2)
C(9)-H(9)	0.90(3)
C(10)-C(21)	1.532(3)
C(10)-C(11)	1.546(3)
C(10)-H(10)	0.97(2)
C(11)-C(13)	1.514(3)
C(11)-C(12)	1.531(3)
C(11)-H(11)	0.97(2)
C(12)-H(12A)	1.00(3)

C(12)-H(12B)	1.03(3)
C(12)-H(12C)	0.93(4)
C(13)-H(13A)	0.98(3)
C(13)-H(13B)	0.94(4)
C(13)-H(13C)	1.04(4)
C(14)-C(15)	1.508(3)
C(14)-H(14A)	0.99(3)
C(14)-H(14B)	0.95(3)
C(15)-C(20)	1.386(3)
C(15)-C(16)	1.389(3)
C(16)-C(17)	1.383(3)
C(16)-H(16)	0.99(3)
C(17)-C(18)	1.378(3)
C(17)-H(17)	0.89(3)
C(18)-C(19)	1.386(3)
C(18)-H(18)	0.93(3)
C(19)-C(20)	1.383(3)
C(19)-H(19)	0.99(3)
C(20)-H(20)	0.93(2)
C(22)-H(22A)	1.03(3)
C(22)-H(22B)	1.01(4)
C(22)-H(22C)	1.00(3)

O(1)-S-O(2)	119.03(9)
O(1)-S-N(1)	107.11(7)
O(2)-S-N(1)	107.64(8)
O(1)-S-C(5)	109.78(9)
O(2)-S-C(5)	106.96(7)
N(1)-S-C(5)	105.54(9)
C(21)-O(3)-C(22)	115.57(18)
C(10)-N(1)-C(1)	120.38(16)
C(10)-N(1)-S	117.64(12)
C(1)-N(1)-S	117.51(14)
N(3)-N(2)-C(2)	109.20(14)
N(2)-N(3)-N(4)	107.65(14)
N(3)-N(4)-C(3)	110.66(16)
N(3)-N(4)-C(14)	117.01(16)
C(3)-N(4)-C(14)	131.65(16)

N(1)-C(1)-C(2)	116.12(15)
N(1)-C(1)-H(1A)	109.1(14)
C(2)-C(1)-H(1A)	108.9(14)
N(1)-C(1)-H(1B)	104.5(14)
C(2)-C(1)-H(1B)	112.8(15)
H(1A)-C(1)-H(1B)	105(2)
N(2)-C(2)-C(3)	108.71(16)
N(2)-C(2)-C(1)	118.09(15)
C(3)-C(2)-C(1)	133.20(16)
N(4)-C(3)-C(2)	103.77(14)
N(4)-C(3)-C(4)	123.46(15)
C(2)-C(3)-C(4)	132.71(16)
C(9)-C(4)-C(5)	116.96(15)
C(9)-C(4)-C(3)	121.26(16)
C(5)-C(4)-C(3)	121.78(14)
C(6)-C(5)-C(4)	121.94(15)
C(6)-C(5)-S	117.76(13)
C(4)-C(5)-S	120.27(12)
C(7)-C(6)-C(5)	119.57(16)
C(7)-C(6)-H(6)	120.2(12)
C(5)-C(6)-H(6)	120.0(12)
C(6)-C(7)-C(8)	119.75(16)
C(6)-C(7)-H(7)	118.7(13)
C(8)-C(7)-H(7)	121.5(13)
C(9)-C(8)-C(7)	120.15(17)
C(9)-C(8)-H(8)	120.1(13)
C(7)-C(8)-H(8)	119.6(13)
C(8)-C(9)-C(4)	121.59(18)
C(8)-C(9)-H(9)	119.5(15)
C(4)-C(9)-H(9)	118.8(15)
N(1)-C(10)-C(21)	110.69(15)
N(1)-C(10)-C(11)	112.81(15)
C(21)-C(10)-C(11)	111.24(17)
N(1)-C(10)-H(10)	104.8(14)
C(21)-C(10)-H(10)	110.2(13)
C(11)-C(10)-H(10)	106.8(13)
C(13)-C(11)-C(12)	110.56(19)
C(13)-C(11)-C(10)	111.16(19)

C(12)-C(11)-C(10)	110.15(16)
C(13)-C(11)-H(11)	109.9(13)
C(12)-C(11)-H(11)	109.6(14)
C(10)-C(11)-H(11)	105.3(13)
C(11)-C(12)-H(12A)	113.9(16)
C(11)-C(12)-H(12B)	111.7(15)
H(12A)-C(12)-H(12B)	107(2)
C(11)-C(12)-H(12C)	112(2)
H(12A)-C(12)-H(12C)	107(3)
H(12B)-C(12)-H(12C)	106(3)
C(11)-C(13)-H(13A)	105.9(17)
C(11)-C(13)-H(13B)	112(2)
H(13A)-C(13)-H(13B)	108(3)
C(11)-C(13)-H(13C)	111(2)
H(13A)-C(13)-H(13C)	114(3)
H(13B)-C(13)-H(13C)	107(3)
N(4)-C(14)-C(15)	113.24(16)
N(4)-C(14)-H(14A)	108.5(15)
C(15)-C(14)-H(14A)	114.0(14)
N(4)-C(14)-H(14B)	105.8(15)
C(15)-C(14)-H(14B)	108.3(16)
H(14A)-C(14)-H(14B)	106(2)
C(20)-C(15)-C(16)	119.05(19)
C(20)-C(15)-C(14)	121.67(18)
C(16)-C(15)-C(14)	119.18(18)
C(17)-C(16)-C(15)	120.1(2)
C(17)-C(16)-H(16)	119.2(16)
C(15)-C(16)-H(16)	120.6(16)
C(18)-C(17)-C(16)	120.8(2)
C(18)-C(17)-H(17)	120.2(17)
C(16)-C(17)-H(17)	119.0(17)
C(17)-C(18)-C(19)	119.4(2)
C(17)-C(18)-H(18)	120.1(15)
C(19)-C(18)-H(18)	120.5(15)
C(20)-C(19)-C(18)	120.0(2)
C(20)-C(19)-H(19)	119.5(16)
C(18)-C(19)-H(19)	120.4(16)
C(19)-C(20)-C(15)	120.68(18)

C(19)-C(20)-H(20)	115.2(16)
C(15)-C(20)-H(20)	124.2(16)
O(4)-C(21)-O(3)	124.87(19)
O(4)-C(21)-C(10)	124.10(18)
O(3)-C(21)-C(10)	111.00(16)
O(3)-C(22)-H(22A)	105.7(16)
O(3)-C(22)-H(22B)	110(2)
H(22A)-C(22)-H(22B)	116(3)
O(3)-C(22)-H(22C)	112.2(18)
H(22A)-C(22)-H(22C)	114(2)
H(22B)-C(22)-H(22C)	98(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C22H24N4O4S. The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ..+ 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	16(1)	20(1)	17(1)	1(1)	7(1)	2(1)
O(1)	23(1)	23(1)	22(1)	3(1)	8(1)	2(1)
O(2)	21(1)	24(1)	22(1)	-1(1)	12(1)	1(1)
O(3)	28(1)	38(1)	27(1)	9(1)	5(1)	2(1)
O(4)	36(1)	43(1)	40(1)	5(1)	21(1)	11(1)
N(1)	24(1)	22(1)	15(1)	0(1)	7(1)	-1(1)
N(2)	41(1)	25(1)	17(1)	-2(1)	13(1)	-6(1)
N(3)	43(1)	27(1)	19(1)	-3(1)	18(1)	-5(1)
N(4)	28(1)	25(1)	21(1)	-4(1)	16(1)	-3(1)
C(1)	27(1)	28(1)	15(1)	0(1)	6(1)	-3(1)
C(2)	29(1)	21(1)	15(1)	0(1)	10(1)	0(1)
C(3)	23(1)	21(1)	19(1)	-1(1)	13(1)	1(1)
C(4)	23(1)	19(1)	18(1)	-3(1)	9(1)	0(1)
C(5)	18(1)	18(1)	18(1)	-2(1)	7(1)	0(1)
C(6)	25(1)	19(1)	19(1)	-1(1)	10(1)	0(1)
C(7)	28(1)	28(1)	17(1)	0(1)	6(1)	2(1)
C(8)	18(1)	32(1)	26(1)	-3(1)	3(1)	3(1)
C(9)	22(1)	30(1)	26(1)	-3(1)	12(1)	3(1)
C(10)	23(1)	23(1)	17(1)	0(1)	8(1)	-1(1)
C(11)	29(1)	29(1)	23(1)	-5(1)	8(1)	-9(1)
C(12)	41(1)	28(1)	29(1)	-5(1)	13(1)	-11(1)
C(13)	26(1)	40(2)	52(1)	0(1)	2(1)	-10(1)
C(14)	31(1)	29(1)	32(1)	-6(1)	22(1)	-7(1)
C(15)	28(1)	21(1)	23(1)	1(1)	16(1)	-2(1)
C(16)	24(1)	30(1)	35(1)	-3(1)	11(1)	3(1)
C(17)	27(1)	30(1)	28(1)	-5(1)	6(1)	-2(1)
C(18)	38(1)	23(1)	23(1)	0(1)	15(1)	2(1)
C(19)	28(1)	28(1)	32(1)	1(1)	14(1)	5(1)
C(20)	24(1)	29(1)	26(1)	-2(1)	9(1)	-1(1)
C(21)	28(1)	21(1)	26(1)	-1(1)	8(1)	-2(1)
C(22)	28(1)	45(2)	50(2)	17(1)	4(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C22H24N4O4S.

	x	y	z	U(eq)
H(1A)	-3980(30)	3200(17)	-880(30)	28(6)
H(1B)	-2990(30)	2326(18)	-470(30)	27(6)
H(6)	-380(30)	3593(18)	5810(20)	21(5)
H(7)	2590(30)	3373(16)	7340(30)	26(6)
H(8)	4640(30)	3347(17)	6080(30)	29(6)
H(9)	3420(30)	3402(17)	3310(30)	32(6)
H(10)	-3320(30)	2086(16)	3060(30)	22(5)
H(11)	-4220(30)	1229(16)	160(30)	19(5)
H(12A)	-5370(40)	50(20)	1250(30)	40(7)
H(12B)	-3300(40)	200(18)	2360(30)	34(6)
H(12C)	-4800(40)	590(30)	2800(40)	64(9)
H(13A)	-6210(40)	2310(20)	-100(30)	40(7)
H(13B)	-7190(50)	1430(20)	-190(40)	62(9)
H(13C)	-6620(50)	1930(30)	1450(50)	83(12)
H(14A)	3730(30)	4137(17)	1510(30)	26(6)
H(14B)	2890(30)	4744(17)	40(30)	27(6)
H(16)	5330(40)	5310(20)	3360(30)	37(7)
H(17)	5190(40)	6561(18)	4690(30)	30(6)
H(18)	2680(30)	7358(18)	4150(30)	27(6)
H(19)	40(40)	6887(19)	2130(30)	35(7)
H(20)	70(30)	5636(17)	810(30)	28(6)
H(22A)	1160(40)	550(20)	5780(30)	44(8)
H(22B)	1900(50)	1220(30)	4660(40)	68(10)
H(22C)	1090(40)	350(20)	3930(40)	47(8)

Table 6. Torsion angles [°] for C22H24N4O4S.

O(1)-S-N(1)-C(10)	-171.55(15)
O(2)-S-N(1)-C(10)	-42.45(15)
C(5)-S-N(1)-C(10)	71.51(15)
O(1)-S-N(1)-C(1)	32.06(15)
O(2)-S-N(1)-C(1)	161.16(13)
C(5)-S-N(1)-C(1)	-84.88(15)
C(2)-N(2)-N(3)-N(4)	0.4(2)
N(2)-N(3)-N(4)-C(3)	-0.6(2)
N(2)-N(3)-N(4)-C(14)	-172.25(18)
C(10)-N(1)-C(1)-C(2)	-116.1(2)
S-N(1)-C(1)-C(2)	39.6(2)
N(3)-N(2)-C(2)-C(3)	-0.1(2)
N(3)-N(2)-C(2)-C(1)	179.58(18)
N(1)-C(1)-C(2)-N(2)	-164.90(18)
N(1)-C(1)-C(2)-C(3)	14.7(3)
N(3)-N(4)-C(3)-C(2)	0.5(2)
C(14)-N(4)-C(3)-C(2)	170.6(2)
N(3)-N(4)-C(3)-C(4)	-177.07(18)
C(14)-N(4)-C(3)-C(4)	-7.0(3)
N(2)-C(2)-C(3)-N(4)	-0.2(2)
C(1)-C(2)-C(3)-N(4)	-179.8(2)
N(2)-C(2)-C(3)-C(4)	177.0(2)
C(1)-C(2)-C(3)-C(4)	-2.6(4)
N(4)-C(3)-C(4)-C(9)	-35.5(3)
C(2)-C(3)-C(4)-C(9)	147.8(2)
N(4)-C(3)-C(4)-C(5)	144.6(2)
C(2)-C(3)-C(4)-C(5)	-32.2(3)
C(9)-C(4)-C(5)-C(6)	0.8(3)
C(3)-C(4)-C(5)-C(6)	-179.23(19)
C(9)-C(4)-C(5)-S	-177.10(16)
C(3)-C(4)-C(5)-S	2.8(3)
O(1)-S-C(5)-C(6)	124.79(16)
O(2)-S-C(5)-C(6)	-5.67(19)
N(1)-S-C(5)-C(6)	-120.10(15)
O(1)-S-C(5)-C(4)	-57.19(18)
O(2)-S-C(5)-C(4)	172.36(15)

N(1)-S-C(5)-C(4)	57.93(18)
C(4)-C(5)-C(6)-C(7)	1.0(3)
S-C(5)-C(6)-C(7)	178.96(15)
C(5)-C(6)-C(7)-C(8)	-1.3(3)
C(6)-C(7)-C(8)-C(9)	-0.3(3)
C(7)-C(8)-C(9)-C(4)	2.2(3)
C(5)-C(4)-C(9)-C(8)	-2.4(3)
C(3)-C(4)-C(9)-C(8)	177.65(19)
C(1)-N(1)-C(10)-C(21)	67.0(2)
S-N(1)-C(10)-C(21)	-88.68(17)
C(1)-N(1)-C(10)-C(11)	-58.4(2)
S-N(1)-C(10)-C(11)	145.94(14)
N(1)-C(10)-C(11)-C(13)	-52.1(2)
C(21)-C(10)-C(11)-C(13)	-177.21(19)
N(1)-C(10)-C(11)-C(12)	-175.04(17)
C(21)-C(10)-C(11)-C(12)	59.9(2)
N(3)-N(4)-C(14)-C(15)	111.98(19)
C(3)-N(4)-C(14)-C(15)	-57.6(3)
N(4)-C(14)-C(15)-C(20)	-34.1(3)
N(4)-C(14)-C(15)-C(16)	149.52(19)
C(20)-C(15)-C(16)-C(17)	-1.3(3)
C(14)-C(15)-C(16)-C(17)	175.1(2)
C(15)-C(16)-C(17)-C(18)	0.3(3)
C(16)-C(17)-C(18)-C(19)	1.2(3)
C(17)-C(18)-C(19)-C(20)	-1.8(3)
C(18)-C(19)-C(20)-C(15)	0.8(3)
C(16)-C(15)-C(20)-C(19)	0.8(3)
C(14)-C(15)-C(20)-C(19)	-175.55(19)
C(22)-O(3)-C(21)-O(4)	-1.3(3)
C(22)-O(3)-C(21)-C(10)	-179.42(19)
N(1)-C(10)-C(21)-O(4)	-44.4(3)
C(11)-C(10)-C(21)-O(4)	81.9(2)
N(1)-C(10)-C(21)-O(3)	133.79(17)
C(11)-C(10)-C(21)-O(3)	-99.95(19)

Symmetry transformations used to generate equivalent atoms:

(*S*)-Methyl 2-((*S*$_a$)-1-benzyl-6,6-dioxido-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-4-methylpentanoate (4.43)

Table 1. Crystal data and structure refinement for C23H26N4O4S.

Empirical formula	C23 H26 N4 O4 S	
Formula weight	454.54	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.0665(5) Å	α= 90°.
	b = 9.2804(3) Å	β= 97.2240(10)°.
	c = 18.3074(7) Å	γ = 90°.
Volume	2202.38(14) Å^3	
Z	4	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	1.628 mm^{-1}	
F(000)	960	
Crystal size	0.23 x 0.16 x 0.09 mm^3	
Theta range for data collection	3.41 to 69.17°.	
Index ranges	-13<=h<=15, -11<=k<=11, -17<=l<=21	
Reflections collected	20135	
Independent reflections	3874 [R(int) = 0.0196]	
Completeness to theta = 66.00°	96.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.778	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3874 / 0 / 394	
Goodness-of-fit on F^2	1.100	
Final R indices [I>2sigma(I)]	R1 = 0.0321, wR2 = 0.0795	
R indices (all data)	R1 = 0.0322, wR2 = 0.0796	
Extinction coefficient	0.00154(19)	
Largest diff. peak and hole	0.327 and -0.380 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C23H26N4O4S.U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	2124(1)	3819(1)	5982(1)	18(1)
O(1)	1986(1)	2314(1)	5830(1)	23(1)
O(2)	1766(1)	4408(1)	6628(1)	24(1)
O(3)	3326(1)	7939(1)	5682(1)	26(1)
O(4)	3845(1)	6252(1)	4926(1)	23(1)
N(1)	3357(1)	4152(1)	6019(1)	19(1)
N(2)	3886(1)	1954(1)	4381(1)	23(1)
N(3)	3332(1)	1827(1)	3734(1)	25(1)
N(4)	2539(1)	2759(1)	3711(1)	20(1)
C(1)	3943(1)	3248(2)	5553(1)	21(1)
C(2)	3444(1)	2962(2)	4780(1)	19(1)
C(3)	2574(1)	3499(2)	4362(1)	18(1)
C(4)	1842(1)	4633(2)	4511(1)	17(1)
C(5)	1574(1)	4874(2)	5223(1)	17(1)
C(6)	955(1)	6022(2)	5373(1)	19(1)
C(7)	560(1)	6948(2)	4810(1)	22(1)
C(8)	802(1)	6719(2)	4106(1)	24(1)
C(9)	1439(1)	5587(2)	3960(1)	21(1)
C(10)	3668(1)	5654(2)	6199(1)	21(1)
C(11)	4748(1)	5757(2)	6630(1)	25(1)
C(12)	4841(1)	5145(2)	7412(1)	28(1)
C(13)	4213(2)	5993(2)	7910(1)	35(1)
C(14)	5981(2)	5144(2)	7728(1)	41(1)
C(15)	1768(1)	2704(2)	3054(1)	24(1)
C(16)	724(1)	2156(2)	3202(1)	21(1)
C(17)	-162(1)	2764(2)	2825(1)	26(1)
C(18)	-1127(1)	2191(2)	2899(1)	30(1)
C(19)	-1217(1)	1026(2)	3356(1)	29(1)
C(20)	-337(1)	435(2)	3746(1)	28(1)
C(21)	630(1)	988(2)	3667(1)	24(1)
C(22)	3626(1)	6616(2)	5517(1)	20(1)
C(23)	3341(2)	9008(2)	5105(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for C23H26N4O4S.

S-O(1)	1.4317(11)
S-O(2)	1.4329(11)
S-N(1)	1.6337(13)
S-C(5)	1.7762(14)
O(3)-C(22)	1.3350(18)
O(3)-C(23)	1.4503(19)
O(4)-C(22)	1.2021(18)
N(1)-C(1)	1.4760(19)
N(1)-C(10)	1.4780(18)
N(2)-N(3)	1.3137(19)
N(2)-C(2)	1.3603(19)
N(3)-N(4)	1.3469(18)
N(4)-C(3)	1.3710(18)
N(4)-C(15)	1.4692(19)
C(1)-C(2)	1.505(2)
C(1)-H(1A)	0.96(2)
C(1)-H(1B)	0.989(18)
C(2)-C(3)	1.381(2)
C(3)-C(4)	1.470(2)
C(4)-C(9)	1.395(2)
C(4)-C(5)	1.4100(19)
C(5)-C(6)	1.386(2)
C(6)-C(7)	1.390(2)
C(6)-H(6)	0.973(18)
C(7)-C(8)	1.383(2)
C(7)-H(7)	0.954(18)
C(8)-C(9)	1.386(2)
C(8)-H(8)	0.97(2)
C(9)-H(9)	0.980(18)
C(10)-C(11)	1.531(2)
C(10)-C(22)	1.531(2)
C(10)-H(10)	1.007(18)
C(11)-C(12)	1.530(2)
C(11)-H(11A)	1.004(19)
C(11)-H(11B)	1.005(19)
C(12)-C(13)	1.522(3)

C(12)-C(14)	1.529(2)
C(12)-H(12)	0.965(19)
C(13)-H(13A)	1.00(2)
C(13)-H(13B)	0.96(2)
C(13)-H(13C)	0.99(2)
C(14)-H(14A)	1.00(2)
C(14)-H(14B)	0.99(2)
C(14)-H(14C)	0.98(3)
C(15)-C(16)	1.511(2)
C(15)-H(15A)	0.934(19)
C(15)-H(15B)	0.998(19)
C(16)-C(17)	1.391(2)
C(16)-C(21)	1.394(2)
C(17)-C(18)	1.391(3)
C(17)-H(17)	0.94(2)
C(18)-C(19)	1.381(3)
C(18)-H(18)	0.97(2)
C(19)-C(20)	1.388(2)
C(19)-H(19)	0.95(2)
C(20)-C(21)	1.388(2)
C(20)-H(20)	0.96(2)
C(21)-H(21)	0.958(19)
C(23)-H(23A)	0.96(2)
C(23)-H(23B)	0.97(2)
C(23)-H(23C)	0.97(2)

O(1)-S-O(2)	119.09(6)
O(1)-S-N(1)	106.99(6)
O(2)-S-N(1)	108.48(6)
O(1)-S-C(5)	110.91(6)
O(2)-S-C(5)	107.02(6)
N(1)-S-C(5)	103.20(6)
C(22)-O(3)-C(23)	115.65(12)
C(1)-N(1)-C(10)	121.19(12)
C(1)-N(1)-S	116.68(10)
C(10)-N(1)-S	115.38(10)
N(3)-N(2)-C(2)	108.88(13)
N(2)-N(3)-N(4)	107.72(11)

N(3)-N(4)-C(3)	110.71(12)
N(3)-N(4)-C(15)	116.64(12)
C(3)-N(4)-C(15)	132.33(13)
N(1)-C(1)-C(2)	116.61(12)
N(1)-C(1)-H(1A)	107.2(11)
C(2)-C(1)-H(1A)	108.5(10)
N(1)-C(1)-H(1B)	107.8(10)
C(2)-C(1)-H(1B)	107.5(10)
H(1A)-C(1)-H(1B)	109.1(14)
N(2)-C(2)-C(3)	109.01(13)
N(2)-C(2)-C(1)	117.59(13)
C(3)-C(2)-C(1)	133.38(13)
N(4)-C(3)-C(2)	103.68(12)
N(4)-C(3)-C(4)	124.63(13)
C(2)-C(3)-C(4)	131.64(13)
C(9)-C(4)-C(5)	116.89(13)
C(9)-C(4)-C(3)	121.05(12)
C(5)-C(4)-C(3)	121.91(12)
C(6)-C(5)-C(4)	121.66(13)
C(6)-C(5)-S	117.25(10)
C(4)-C(5)-S	120.80(11)
C(5)-C(6)-C(7)	119.95(13)
C(5)-C(6)-H(6)	119.4(10)
C(7)-C(6)-H(6)	120.6(10)
C(8)-C(7)-C(6)	119.34(14)
C(8)-C(7)-H(7)	120.7(11)
C(6)-C(7)-H(7)	119.9(11)
C(7)-C(8)-C(9)	120.55(14)
C(7)-C(8)-H(8)	120.4(11)
C(9)-C(8)-H(8)	119.0(11)
C(8)-C(9)-C(4)	121.60(13)
C(8)-C(9)-H(9)	118.8(10)
C(4)-C(9)-H(9)	119.6(10)
N(1)-C(10)-C(11)	112.54(12)
N(1)-C(10)-C(22)	112.79(11)
C(11)-C(10)-C(22)	108.65(12)
N(1)-C(10)-H(10)	105.3(10)
C(11)-C(10)-H(10)	108.9(10)

C(22)-C(10)-H(10)	108.5(10)
C(12)-C(11)-C(10)	114.76(13)
C(12)-C(11)-H(11A)	110.3(10)
C(10)-C(11)-H(11A)	108.3(11)
C(12)-C(11)-H(11B)	107.2(10)
C(10)-C(11)-H(11B)	107.5(10)
H(11A)-C(11)-H(11B)	108.6(15)
C(13)-C(12)-C(14)	110.26(15)
C(13)-C(12)-C(11)	112.56(14)
C(14)-C(12)-C(11)	108.31(15)
C(13)-C(12)-H(12)	110.4(11)
C(14)-C(12)-H(12)	108.8(11)
C(11)-C(12)-H(12)	106.4(11)
C(12)-C(13)-H(13A)	112.5(11)
C(12)-C(13)-H(13B)	112.0(13)
H(13A)-C(13)-H(13B)	108.0(16)
C(12)-C(13)-H(13C)	110.8(13)
H(13A)-C(13)-H(13C)	107.7(17)
H(13B)-C(13)-H(13C)	105.4(18)
C(12)-C(14)-H(14A)	108.6(11)
C(12)-C(14)-H(14B)	109.5(12)
H(14A)-C(14)-H(14B)	109.3(16)
C(12)-C(14)-H(14C)	109.4(15)
H(14A)-C(14)-H(14C)	111.3(18)
H(14B)-C(14)-H(14C)	108.7(19)
N(4)-C(15)-C(16)	113.98(12)
N(4)-C(15)-H(15A)	105.0(11)
C(16)-C(15)-H(15A)	109.2(11)
N(4)-C(15)-H(15B)	109.9(10)
C(16)-C(15)-H(15B)	111.2(10)
H(15A)-C(15)-H(15B)	107.2(14)
C(17)-C(16)-C(21)	119.11(15)
C(17)-C(16)-C(15)	119.26(14)
C(21)-C(16)-C(15)	121.47(14)
C(18)-C(17)-C(16)	120.32(15)
C(18)-C(17)-H(17)	121.0(12)
C(16)-C(17)-H(17)	118.7(12)
C(19)-C(18)-C(17)	120.37(16)

C(19)-C(18)-H(18)	120.0(12)
C(17)-C(18)-H(18)	119.6(12)
C(18)-C(19)-C(20)	119.54(16)
C(18)-C(19)-H(19)	120.7(12)
C(20)-C(19)-H(19)	119.8(12)
C(21)-C(20)-C(19)	120.44(16)
C(21)-C(20)-H(20)	120.5(12)
C(19)-C(20)-H(20)	119.1(12)
C(20)-C(21)-C(16)	120.20(15)
C(20)-C(21)-H(21)	120.1(11)
C(16)-C(21)-H(21)	119.7(11)
O(4)-C(22)-O(3)	124.92(13)
O(4)-C(22)-C(10)	125.63(13)
O(3)-C(22)-C(10)	109.44(12)
O(3)-C(23)-H(23A)	108.5(13)
O(3)-C(23)-H(23B)	104.8(12)
H(23A)-C(23)-H(23B)	110.5(18)
O(3)-C(23)-H(23C)	109.6(13)
H(23A)-C(23)-H(23C)	111.8(18)
H(23B)-C(23)-H(23C)	111.4(18)

Symmetry transformations used to generate equivalent atoms:

Table 4.Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C23H26N4O4S. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	20(1)	18(1)	15(1)	4(1)	1(1)	0(1)
O(1)	23(1)	18(1)	27(1)	5(1)	2(1)	-2(1)
O(2)	27(1)	29(1)	16(1)	4(1)	3(1)	1(1)
O(3)	34(1)	17(1)	26(1)	4(1)	4(1)	1(1)
O(4)	24(1)	23(1)	23(1)	1(1)	3(1)	-3(1)
N(1)	21(1)	17(1)	18(1)	2(1)	-1(1)	-1(1)
N(2)	25(1)	17(1)	29(1)	0(1)	7(1)	1(1)
N(3)	28(1)	19(1)	28(1)	-4(1)	9(1)	1(1)
N(4)	23(1)	19(1)	20(1)	-3(1)	5(1)	-1(1)
C(1)	18(1)	21(1)	24(1)	2(1)	1(1)	2(1)
C(2)	20(1)	15(1)	23(1)	2(1)	6(1)	-2(1)
C(3)	22(1)	16(1)	16(1)	-1(1)	5(1)	-3(1)
C(4)	18(1)	16(1)	17(1)	-2(1)	1(1)	-3(1)
C(5)	18(1)	17(1)	16(1)	1(1)	0(1)	-3(1)
C(6)	20(1)	21(1)	16(1)	-2(1)	2(1)	-1(1)
C(7)	23(1)	20(1)	23(1)	-2(1)	1(1)	4(1)
C(8)	29(1)	23(1)	18(1)	3(1)	-2(1)	4(1)
C(9)	26(1)	23(1)	15(1)	-1(1)	1(1)	0(1)
C(10)	24(1)	19(1)	20(1)	1(1)	0(1)	-2(1)
C(11)	24(1)	24(1)	24(1)	1(1)	-1(1)	-3(1)
C(12)	34(1)	22(1)	26(1)	5(1)	-7(1)	-8(1)
C(13)	47(1)	32(1)	26(1)	3(1)	3(1)	-11(1)
C(14)	38(1)	41(1)	41(1)	10(1)	-11(1)	-5(1)
C(15)	30(1)	24(1)	16(1)	-5(1)	4(1)	-3(1)
C(16)	28(1)	20(1)	16(1)	-7(1)	2(1)	0(1)
C(17)	36(1)	25(1)	16(1)	-4(1)	0(1)	4(1)
C(18)	28(1)	37(1)	24(1)	-12(1)	-3(1)	6(1)
C(19)	25(1)	32(1)	31(1)	-15(1)	6(1)	-4(1)
C(20)	33(1)	21(1)	30(1)	-4(1)	7(1)	-3(1)
C(21)	27(1)	20(1)	25(1)	-3(1)	2(1)	2(1)
C(22)	17(1)	18(1)	23(1)	1(1)	-1(1)	-4(1)
C(23)	45(1)	21(1)	34(1)	10(1)	5(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C23H26N4O4S.

	x	y	z	U(eq)
H(1A)	4592(15)	3715(19)	5529(9)	25(4)
H(1B)	4066(13)	2305(19)	5801(10)	23(4)
H(6)	787(14)	6158(18)	5872(10)	25(4)
H(7)	120(14)	7724(19)	4911(10)	24(4)
H(8)	548(15)	7370(20)	3708(11)	33(5)
H(9)	1627(13)	5481(18)	3461(10)	22(4)
H(10)	3149(14)	6022(18)	6518(9)	22(4)
H(11A)	5246(14)	5260(20)	6338(10)	27(4)
H(11B)	4935(14)	6810(20)	6674(10)	26(4)
H(12)	4602(14)	4160(20)	7365(10)	26(4)
H(13A)	3455(17)	5910(20)	7757(11)	33(5)
H(13B)	4351(16)	5690(20)	8415(12)	40(5)
H(13C)	4394(17)	7030(30)	7912(12)	46(6)
H(14A)	6378(15)	4590(20)	7386(11)	32(5)
H(14B)	6238(15)	6140(20)	7768(11)	34(5)
H(14C)	6058(19)	4710(30)	8222(14)	62(7)
H(15A)	2043(14)	2072(19)	2733(10)	23(4)
H(15B)	1711(14)	3670(20)	2811(10)	25(4)
H(17)	-96(15)	3590(20)	2536(11)	30(5)
H(18)	-1741(16)	2620(20)	2633(11)	34(5)
H(19)	-1875(16)	650(20)	3419(10)	30(5)
H(20)	-406(15)	-360(20)	4069(11)	35(5)
H(21)	1236(15)	560(20)	3927(10)	27(4)
H(23A)	4044(18)	9200(20)	5044(11)	40(6)
H(23B)	3019(16)	9850(20)	5289(11)	40(5)
H(23C)	2954(17)	8660(20)	4655(13)	43(6)

Table 6. Torsion angles [°] for C23H26N4O4S.

O(1)-S-N(1)-C(1)	30.51(11)
O(2)-S-N(1)-C(1)	160.16(10)
C(5)-S-N(1)-C(1)	-86.55(11)
O(1)-S-N(1)-C(10)	-177.85(9)
O(2)-S-N(1)-C(10)	-48.20(11)
C(5)-S-N(1)-C(10)	65.08(11)
C(2)-N(2)-N(3)-N(4)	0.52(16)
N(2)-N(3)-N(4)-C(3)	-0.52(16)
N(2)-N(3)-N(4)-C(15)	-174.88(12)
C(10)-N(1)-C(1)-C(2)	-106.62(15)
S-N(1)-C(1)-C(2)	43.27(16)
N(3)-N(2)-C(2)-C(3)	-0.34(16)
N(3)-N(2)-C(2)-C(1)	178.37(12)
N(1)-C(1)-C(2)-N(2)	-169.77(12)
N(1)-C(1)-C(2)-C(3)	8.6(2)
N(3)-N(4)-C(3)-C(2)	0.30(15)
C(15)-N(4)-C(3)-C(2)	173.47(14)
N(3)-N(4)-C(3)-C(4)	177.80(13)
C(15)-N(4)-C(3)-C(4)	-9.0(2)
N(2)-C(2)-C(3)-N(4)	0.02(15)
C(1)-C(2)-C(3)-N(4)	-178.41(15)
N(2)-C(2)-C(3)-C(4)	-177.22(14)
C(1)-C(2)-C(3)-C(4)	4.3(3)
N(4)-C(3)-C(4)-C(9)	-35.8(2)
C(2)-C(3)-C(4)-C(9)	140.95(16)
N(4)-C(3)-C(4)-C(5)	148.84(14)
C(2)-C(3)-C(4)-C(5)	-34.4(2)
C(9)-C(4)-C(5)-C(6)	-1.3(2)
C(3)-C(4)-C(5)-C(6)	174.29(13)
C(9)-C(4)-C(5)-S	-174.88(11)
C(3)-C(4)-C(5)-S	0.66(19)
O(1)-S-C(5)-C(6)	132.66(11)
O(2)-S-C(5)-C(6)	1.26(13)
N(1)-S-C(5)-C(6)	-113.09(12)
O(1)-S-C(5)-C(4)	-53.44(13)
O(2)-S-C(5)-C(4)	175.16(11)

N(1)-S-C(5)-C(4)	60.82(13)
C(4)-C(5)-C(6)-C(7)	1.7(2)
S-C(5)-C(6)-C(7)	175.51(11)
C(5)-C(6)-C(7)-C(8)	-0.7(2)
C(6)-C(7)-C(8)-C(9)	-0.6(2)
C(7)-C(8)-C(9)-C(4)	1.0(2)
C(5)-C(4)-C(9)-C(8)	-0.1(2)
C(3)-C(4)-C(9)-C(8)	-175.65(14)
C(1)-N(1)-C(10)-C(11)	-61.55(16)
S-N(1)-C(10)-C(11)	148.20(11)
C(1)-N(1)-C(10)-C(22)	61.81(17)
S-N(1)-C(10)-C(22)	-88.44(13)
N(1)-C(10)-C(11)-C(12)	-67.98(17)
C(22)-C(10)-C(11)-C(12)	166.39(13)
C(10)-C(11)-C(12)-C(13)	-65.26(18)
C(10)-C(11)-C(12)-C(14)	172.57(15)
N(3)-N(4)-C(15)-C(16)	111.94(14)
C(3)-N(4)-C(15)-C(16)	-60.9(2)
N(4)-C(15)-C(16)-C(17)	142.90(14)
N(4)-C(15)-C(16)-C(21)	-41.82(19)
C(21)-C(16)-C(17)-C(18)	-1.4(2)
C(15)-C(16)-C(17)-C(18)	173.95(13)
C(16)-C(17)-C(18)-C(19)	1.0(2)
C(17)-C(18)-C(19)-C(20)	0.3(2)
C(18)-C(19)-C(20)-C(21)	-1.2(2)
C(19)-C(20)-C(21)-C(16)	0.8(2)
C(17)-C(16)-C(21)-C(20)	0.5(2)
C(15)-C(16)-C(21)-C(20)	-174.75(13)
C(23)-O(3)-C(22)-O(4)	-4.3(2)
C(23)-O(3)-C(22)-C(10)	174.62(13)
N(1)-C(10)-C(22)-O(4)	-36.4(2)
C(11)-C(10)-C(22)-O(4)	89.08(17)
N(1)-C(10)-C(22)-O(3)	144.66(13)
C(11)-C(10)-C(22)-O(3)	-89.85(15)

Symmetry transformations used to generate equivalent atoms:

(*S*)-Methyl 2-(1-benzyl-7,7-dioxido-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.64)

Table 1. Crystal data and structure refinement for C23H26N4O4S.

Empirical formula	C23 H26 N4 O4 S	
Formula weight	454.54	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.3721(2) Å	α= 90°.
	b = 13.0470(3) Å	β= 100.8540(10)°.
	c = 21.4511(5) Å	γ = 90°.
Volume	2301.20(9) $Å^3$	
Z	4	
Density (calculated)	1.312 Mg/m^3	
Absorption coefficient	1.558 mm^{-1}	
F(000)	960	
Crystal size	0.22 x 0.02 x 0.02 mm^3	
Theta range for data collection	3.99 to 69.32°.	
Index ranges	-10<=h<=9, -15<=k<=14, -21<=l<=26	
Reflections collected	23825	
Independent reflections	4227 [R(int) = 0.0224]	
Completeness to theta = 69.32°	98.2 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.880	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4227 / 0 / 292	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0333, wR2 = 0.0852	
R indices (all data)	R1 = 0.0352, wR2 = 0.0865	
Largest diff. peak and hole	0.448 and -0.306 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for C23H26N4O4S. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	230(1)	2774(1)	1853(1)	19(1)
O(1)	1715(1)	2219(1)	1872(1)	22(1)
O(2)	-50(1)	3284(1)	2414(1)	24(1)
O(3)	-3488(1)	3604(1)	764(1)	32(1)
O(4)	-2394(1)	4681(1)	147(1)	34(1)
N(1)	151(1)	3646(1)	1299(1)	21(1)
N(2)	1866(1)	1122(1)	226(1)	22(1)
N(3)	1963(1)	192(1)	468(1)	22(1)
N(4)	827(1)	122(1)	835(1)	20(1)
C(1)	1053(2)	3516(1)	777(1)	23(1)
C(2)	328(2)	2742(1)	260(1)	24(1)
C(3)	674(2)	1649(1)	441(1)	21(1)
C(4)	-5(2)	1015(1)	834(1)	20(1)
C(5)	-1394(2)	1161(1)	1159(1)	20(1)
C(6)	-1434(2)	1934(1)	1610(1)	20(1)
C(7)	-2819(2)	2092(1)	1872(1)	23(1)
C(8)	-4171(2)	1474(1)	1688(1)	26(1)
C(9)	-4136(2)	690(1)	1254(1)	28(1)
C(10)	-2761(2)	533(1)	992(1)	25(1)
C(11)	-1090(2)	4458(1)	1252(1)	23(1)
C(12)	-2388(2)	4284(1)	654(1)	25(1)
C(13)	-377(2)	5542(1)	1265(1)	29(1)
C(14)	-1700(2)	6320(1)	1342(1)	36(1)
C(15)	1099(2)	5662(1)	1792(1)	39(1)
C(16)	-4703(2)	3288(2)	224(1)	39(1)
C(17)	782(2)	-811(1)	1216(1)	24(1)
C(18)	2397(2)	-969(1)	1654(1)	25(1)
C(19)	2855(2)	-300(1)	2166(1)	28(1)
C(20)	4342(2)	-404(1)	2574(1)	36(1)
C(21)	5388(2)	-1173(2)	2473(1)	43(1)
C(22)	4981(2)	-1839(2)	1975(1)	43(1)
C(23)	3464(2)	-1737(1)	1560(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for C23H26N4O4S.

S-O(2)	1.4317(10)
S-O(1)	1.4326(10)
S-N(1)	1.6374(12)
S-C(6)	1.7719(14)
O(3)-C(12)	1.3313(19)
O(3)-C(16)	1.451(2)
O(4)-C(12)	1.2040(19)
N(1)-C(1)	1.4734(18)
N(1)-C(11)	1.4747(18)
N(2)-N(3)	1.3162(18)
N(2)-C(3)	1.3617(18)
N(3)-N(4)	1.3477(16)
N(4)-C(4)	1.3585(19)
N(4)-C(17)	1.4697(18)
C(1)-C(2)	1.539(2)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.493(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.377(2)
C(4)-C(5)	1.4757(19)
C(5)-C(10)	1.398(2)
C(5)-C(6)	1.403(2)
C(6)-C(7)	1.396(2)
C(7)-C(8)	1.385(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.387(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.388(2)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-C(13)	1.533(2)
C(11)-C(12)	1.534(2)
C(11)-H(11)	1.0000
C(13)-C(15)	1.518(2)

C(13)-C(14)	1.534(2)
C(13)-H(13)	1.0000
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-C(18)	1.507(2)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(23)	1.382(2)
C(18)-C(19)	1.398(2)
C(19)-C(20)	1.387(2)
C(19)-H(19)	0.9500
C(20)-C(21)	1.374(3)
C(20)-H(20)	0.9500
C(21)-C(22)	1.370(3)
C(21)-H(21)	0.9500
C(22)-C(23)	1.414(3)
C(22)-H(22)	0.9500
C(23)-H(23)	0.9500

O(2)-S-O(1)	119.33(6)
O(2)-S-N(1)	107.19(6)
O(1)-S-N(1)	106.75(6)
O(2)-S-C(6)	106.92(6)
O(1)-S-C(6)	109.02(6)
N(1)-S-C(6)	107.05(6)
C(12)-O(3)-C(16)	116.89(13)
C(1)-N(1)-C(11)	119.07(11)
C(1)-N(1)-S	121.01(10)
C(11)-N(1)-S	118.76(9)
N(3)-N(2)-C(3)	109.06(11)
N(2)-N(3)-N(4)	107.17(11)

N(3)-N(4)-C(4)	111.01(11)
N(3)-N(4)-C(17)	118.47(12)
C(4)-N(4)-C(17)	130.14(12)
N(1)-C(1)-C(2)	115.74(12)
N(1)-C(1)-H(1A)	108.3
C(2)-C(1)-H(1A)	108.3
N(1)-C(1)-H(1B)	108.3
C(2)-C(1)-H(1B)	108.3
H(1A)-C(1)-H(1B)	107.4
C(3)-C(2)-C(1)	114.07(12)
C(3)-C(2)-H(2A)	108.7
C(1)-C(2)-H(2A)	108.7
C(3)-C(2)-H(2B)	108.7
C(1)-C(2)-H(2B)	108.7
H(2A)-C(2)-H(2B)	107.6
N(2)-C(3)-C(4)	108.55(13)
N(2)-C(3)-C(2)	120.80(12)
C(4)-C(3)-C(2)	130.62(13)
N(4)-C(4)-C(3)	104.22(12)
N(4)-C(4)-C(5)	123.98(12)
C(3)-C(4)-C(5)	131.64(13)
C(10)-C(5)-C(6)	118.25(13)
C(10)-C(5)-C(4)	118.89(13)
C(6)-C(5)-C(4)	122.80(12)
C(7)-C(6)-C(5)	120.91(13)
C(7)-C(6)-S	117.19(11)
C(5)-C(6)-S	121.87(10)
C(8)-C(7)-C(6)	119.67(14)
C(8)-C(7)-H(7)	120.2
C(6)-C(7)-H(7)	120.2
C(7)-C(8)-C(9)	120.13(13)
C(7)-C(8)-H(8)	119.9
C(9)-C(8)-H(8)	119.9
C(8)-C(9)-C(10)	120.27(14)
C(8)-C(9)-H(9)	119.9
C(10)-C(9)-H(9)	119.9
C(9)-C(10)-C(5)	120.73(14)
C(9)-C(10)-H(10)	119.6

C(5)-C(10)-H(10)	119.6
N(1)-C(11)-C(13)	113.28(12)
N(1)-C(11)-C(12)	109.24(12)
C(13)-C(11)-C(12)	111.36(12)
N(1)-C(11)-H(11)	107.6
C(13)-C(11)-H(11)	107.6
C(12)-C(11)-H(11)	107.6
O(4)-C(12)-O(3)	124.16(14)
O(4)-C(12)-C(11)	124.98(14)
O(3)-C(12)-C(11)	110.83(12)
C(15)-C(13)-C(11)	111.59(13)
C(15)-C(13)-C(14)	110.77(14)
C(11)-C(13)-C(14)	108.99(13)
C(15)-C(13)-H(13)	108.5
C(11)-C(13)-H(13)	108.5
C(14)-C(13)-H(13)	108.5
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(13)-C(15)-H(15A)	109.5
C(13)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(13)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(3)-C(16)-H(16A)	109.5
O(3)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(3)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
N(4)-C(17)-C(18)	110.21(11)
N(4)-C(17)-H(17A)	109.6
C(18)-C(17)-H(17A)	109.6
N(4)-C(17)-H(17B)	109.6

C(18)-C(17)-H(17B)	109.6
H(17A)-C(17)-H(17B)	108.1
C(23)-C(18)-C(19)	118.52(15)
C(23)-C(18)-C(17)	122.47(15)
C(19)-C(18)-C(17)	119.00(13)
C(20)-C(19)-C(18)	121.02(16)
C(20)-C(19)-H(19)	119.5
C(18)-C(19)-H(19)	119.5
C(21)-C(20)-C(19)	119.70(18)
C(21)-C(20)-H(20)	120.2
C(19)-C(20)-H(20)	120.2
C(22)-C(21)-C(20)	120.83(17)
C(22)-C(21)-H(21)	119.6
C(20)-C(21)-H(21)	119.6
C(21)-C(22)-C(23)	119.60(17)
C(21)-C(22)-H(22)	120.2
C(23)-C(22)-H(22)	120.2
C(18)-C(23)-C(22)	120.34(17)
C(18)-C(23)-H(23)	119.8
C(22)-C(23)-H(23)	119.8

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C23H26N4O4S. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	18(1)	19(1)	19(1)	1(1)	3(1)	-1(1)
O(1)	19(1)	23(1)	25(1)	0(1)	2(1)	0(1)
O(2)	28(1)	25(1)	20(1)	-1(1)	5(1)	0(1)
O(3)	24(1)	37(1)	33(1)	9(1)	0(1)	-4(1)
O(4)	33(1)	39(1)	28(1)	9(1)	4(1)	-1(1)
N(1)	21(1)	20(1)	22(1)	2(1)	6(1)	0(1)
N(2)	21(1)	24(1)	21(1)	0(1)	5(1)	-1(1)
N(3)	20(1)	26(1)	21(1)	0(1)	6(1)	-1(1)
N(4)	18(1)	23(1)	19(1)	-1(1)	3(1)	-3(1)
C(1)	23(1)	22(1)	25(1)	2(1)	9(1)	-2(1)
C(2)	27(1)	24(1)	21(1)	2(1)	7(1)	1(1)
C(3)	19(1)	25(1)	18(1)	-2(1)	4(1)	-2(1)
C(4)	18(1)	22(1)	19(1)	-2(1)	2(1)	-2(1)
C(5)	18(1)	23(1)	20(1)	3(1)	4(1)	-1(1)
C(6)	19(1)	20(1)	20(1)	4(1)	4(1)	-1(1)
C(7)	23(1)	22(1)	24(1)	4(1)	8(1)	2(1)
C(8)	20(1)	28(1)	33(1)	7(1)	11(1)	1(1)
C(9)	19(1)	29(1)	34(1)	4(1)	5(1)	-5(1)
C(10)	24(1)	26(1)	25(1)	-1(1)	5(1)	-4(1)
C(11)	24(1)	22(1)	24(1)	3(1)	6(1)	3(1)
C(12)	23(1)	24(1)	28(1)	4(1)	7(1)	5(1)
C(13)	38(1)	21(1)	28(1)	2(1)	7(1)	0(1)
C(14)	51(1)	25(1)	35(1)	3(1)	12(1)	7(1)
C(15)	45(1)	26(1)	42(1)	-2(1)	-1(1)	-10(1)
C(16)	26(1)	45(1)	41(1)	5(1)	-6(1)	-6(1)
C(17)	25(1)	22(1)	24(1)	1(1)	4(1)	-5(1)
C(18)	22(1)	24(1)	30(1)	9(1)	10(1)	1(1)
C(19)	24(1)	28(1)	30(1)	7(1)	3(1)	-2(1)
C(20)	30(1)	36(1)	39(1)	10(1)	-2(1)	-6(1)
C(21)	25(1)	44(1)	60(1)	20(1)	5(1)	1(1)
C(22)	32(1)	38(1)	64(1)	21(1)	22(1)	14(1)
C(23)	40(1)	29(1)	45(1)	6(1)	21(1)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C23H26N4O4S.

	x	y	z	U(eq)
H(1A)	2176	3298	961	27
H(1B)	1125	4191	574	27
H(2A)	-866	2841	156	28
H(2B)	765	2890	-129	28
H(7)	-2835	2621	2175	27
H(8)	-5123	1587	1859	31
H(9)	-5058	259	1135	33
H(10)	-2749	-6	695	30
H(11)	-1633	4390	1627	28
H(13)	-35	5673	850	35
H(14A)	-1280	7017	1317	54
H(14B)	-2016	6221	1755	54
H(14C)	-2650	6219	1003	54
H(15A)	1985	5230	1702	59
H(15B)	816	5454	2197	59
H(15C)	1447	6381	1819	59
H(16A)	-5314	2703	344	59
H(16B)	-4167	3090	-127	59
H(16C)	-5451	3858	89	59
H(17A)	533	-1410	932	28
H(17B)	-88	-749	1469	28
H(19)	2136	233	2235	33
H(20)	4636	54	2921	44
H(21)	6407	-1242	2753	52
H(22)	5713	-2367	1910	52
H(23)	3177	-2198	1214	43

Table 6. Torsion angles [°] for C23H26N4O4S.

O(2)-S-N(1)-C(1)	152.67(10)
O(1)-S-N(1)-C(1)	23.73(12)
C(6)-S-N(1)-C(1)	-92.90(11)
O(2)-S-N(1)-C(11)	-39.75(12)
O(1)-S-N(1)-C(11)	-168.69(10)
C(6)-S-N(1)-C(11)	74.68(11)
C(3)-N(2)-N(3)-N(4)	0.25(15)
N(2)-N(3)-N(4)-C(4)	-0.29(15)
N(2)-N(3)-N(4)-C(17)	-173.88(11)
C(11)-N(1)-C(1)-C(2)	-92.49(15)
S-N(1)-C(1)-C(2)	75.06(15)
N(1)-C(1)-C(2)-C(3)	-78.52(16)
N(3)-N(2)-C(3)-C(4)	-0.12(15)
N(3)-N(2)-C(3)-C(2)	178.05(12)
C(1)-C(2)-C(3)-N(2)	-101.15(15)
C(1)-C(2)-C(3)-C(4)	76.56(19)
N(3)-N(4)-C(4)-C(3)	0.22(15)
C(17)-N(4)-C(4)-C(3)	172.83(13)
N(3)-N(4)-C(4)-C(5)	176.04(12)
C(17)-N(4)-C(4)-C(5)	-11.3(2)
N(2)-C(3)-C(4)-N(4)	-0.06(15)
C(2)-C(3)-C(4)-N(4)	-177.98(14)
N(2)-C(3)-C(4)-C(5)	-175.43(14)
C(2)-C(3)-C(4)-C(5)	6.6(3)
N(4)-C(4)-C(5)-C(10)	-58.72(19)
C(3)-C(4)-C(5)-C(10)	115.86(17)
N(4)-C(4)-C(5)-C(6)	124.30(15)
C(3)-C(4)-C(5)-C(6)	-61.1(2)
C(10)-C(5)-C(6)-C(7)	-1.7(2)
C(4)-C(5)-C(6)-C(7)	175.29(13)
C(10)-C(5)-C(6)-S	-179.78(11)
C(4)-C(5)-C(6)-S	-2.79(19)
O(2)-S-C(6)-C(7)	15.63(13)
O(1)-S-C(6)-C(7)	145.91(11)
N(1)-S-C(6)-C(7)	-98.97(11)
O(2)-S-C(6)-C(5)	-166.22(11)

O(1)-S-C(6)-C(5)	-35.94(13)
N(1)-S-C(6)-C(5)	79.18(12)
C(5)-C(6)-C(7)-C(8)	0.4(2)
S-C(6)-C(7)-C(8)	178.52(11)
C(6)-C(7)-C(8)-C(9)	1.2(2)
C(7)-C(8)-C(9)-C(10)	-1.3(2)
C(8)-C(9)-C(10)-C(5)	-0.1(2)
C(6)-C(5)-C(10)-C(9)	1.6(2)
C(4)-C(5)-C(10)-C(9)	-175.54(13)
C(1)-N(1)-C(11)-C(13)	-66.04(16)
S-N(1)-C(11)-C(13)	126.13(11)
C(1)-N(1)-C(11)-C(12)	58.73(16)
S-N(1)-C(11)-C(12)	-109.10(12)
C(16)-O(3)-C(12)-O(4)	3.7(2)
C(16)-O(3)-C(12)-C(11)	-174.23(13)
N(1)-C(11)-C(12)-O(4)	-94.85(17)
C(13)-C(11)-C(12)-O(4)	31.0(2)
N(1)-C(11)-C(12)-O(3)	83.02(14)
C(13)-C(11)-C(12)-O(3)	-151.10(13)
N(1)-C(11)-C(13)-C(15)	-46.64(18)
C(12)-C(11)-C(13)-C(15)	-170.26(13)
N(1)-C(11)-C(13)-C(14)	-169.29(12)
C(12)-C(11)-C(13)-C(14)	67.09(16)
N(3)-N(4)-C(17)-C(18)	57.82(16)
C(4)-N(4)-C(17)-C(18)	-114.33(15)
N(4)-C(17)-C(18)-C(23)	-108.27(16)
N(4)-C(17)-C(18)-C(19)	70.12(17)
C(23)-C(18)-C(19)-C(20)	-0.3(2)
C(17)-C(18)-C(19)-C(20)	-178.76(14)
C(18)-C(19)-C(20)-C(21)	0.3(2)
C(19)-C(20)-C(21)-C(22)	0.0(3)
C(20)-C(21)-C(22)-C(23)	-0.1(3)
C(19)-C(18)-C(23)-C(22)	0.1(2)
C(17)-C(18)-C(23)-C(22)	178.53(14)
C(21)-C(22)-C(23)-C(18)	0.1(3)

Symmetry transformations used to generate equivalent atoms:

(2*S*)-Methyl 2-(6,6-dioxido-1-phenyl-1*H*-benzo[*f*][1,2,3]triazolo[4,5-*d*][1,2]thiazepin-5(4*H*)-yl)-3-methylbutanoate (4.87)

Table 1. Crystal data and structure refinement for C21H22N4O4S.

Empirical formula	C21 H22 N4 O4 S	
Formula weight	426.49	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.3318(6) Å	α= 90°.
	b = 14.0777(8) Å	β= 90°.
	c = 14.2472(8) Å	γ = 90°.
Volume	2072.2(2) $Å^3$	
Z	4	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	1.695 mm^{-1}	
F(000)	896	
Crystal size	0.07 x 0.05 x 0.03 mm^3	
Theta range for data collection	4.42 to 69.46°.	
Index ranges	-9<=h<=12, -17<=k<=14, -16<=l<=17	
Reflections collected	16995	
Independent reflections	3766 [R(int) = 0.0295]	
Completeness to theta = 66.00°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.928	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3766 / 0 / 359	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0228, wR2 = 0.0606	
R indices (all data)	R1 = 0.0238, wR2 = 0.0611	
Absolute structure parameter	0.043(10)	
Largest diff. peak and hole	0.263 and -0.206 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C21H22N4O4S. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	3608(1)	1209(1)	1933(1)	14(1)
O(1)	3075(1)	589(1)	2634(1)	18(1)
O(2)	4921(1)	1075(1)	1643(1)	19(1)
O(3)	1228(1)	2714(1)	182(1)	29(1)
O(4)	3199(1)	3312(1)	-102(1)	22(1)
N(1)	2664(1)	1137(1)	1017(1)	15(1)
N(2)	-487(1)	1086(1)	2330(1)	18(1)
N(3)	-797(1)	1584(1)	3077(1)	18(1)
N(4)	151(1)	2233(1)	3210(1)	16(1)
C(1)	1282(1)	906(1)	1172(1)	16(1)
C(2)	664(1)	1406(1)	1987(1)	16(1)
C(3)	1085(1)	2149(1)	2539(1)	15(1)
C(4)	2220(1)	2777(1)	2482(1)	16(1)
C(5)	3453(1)	2415(1)	2276(1)	16(1)
C(6)	4527(2)	2998(1)	2231(1)	21(1)
C(7)	4392(2)	3968(1)	2395(1)	25(1)
C(8)	3175(2)	4344(1)	2574(1)	23(1)
C(9)	2099(1)	3759(1)	2616(1)	19(1)
C(10)	3088(1)	1663(1)	174(1)	15(1)
C(11)	2949(1)	1038(1)	-714(1)	18(1)
C(12)	3251(2)	1614(1)	-1601(1)	27(1)
C(13)	3862(2)	189(1)	-637(1)	24(1)
C(14)	183(1)	2776(1)	4064(1)	16(1)
C(15)	1308(2)	2786(1)	4596(1)	21(1)
C(16)	1345(2)	3308(1)	5423(1)	24(1)
C(17)	256(2)	3794(1)	5723(1)	23(1)
C(18)	-866(2)	3770(1)	5193(1)	22(1)
C(19)	-911(2)	3266(1)	4350(1)	18(1)
C(20)	2378(1)	2610(1)	89(1)	18(1)
C(21)	2618(2)	4244(1)	-220(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for C21H22N4O4S.

S-O(2)	1.4315(10)
S-O(1)	1.4360(10)
S-N(1)	1.6325(11)
S-C(5)	1.7741(13)
O(3)-C(20)	1.2045(18)
O(4)-C(20)	1.3295(17)
O(4)-C(21)	1.4531(17)
N(1)-C(10)	1.4781(16)
N(1)-C(1)	1.4801(18)
N(2)-N(3)	1.3139(17)
N(2)-C(2)	1.3625(18)
N(3)-N(4)	1.3534(16)
N(4)-C(3)	1.3645(18)
N(4)-C(14)	1.4374(17)
C(1)-C(2)	1.5014(19)
C(1)-H(1A)	0.944(18)
C(1)-H(1B)	0.919(19)
C(2)-C(3)	1.3779(19)
C(3)-C(4)	1.4708(19)
C(4)-C(9)	1.4016(19)
C(4)-C(5)	1.4022(19)
C(5)-C(6)	1.382(2)
C(6)-C(7)	1.392(2)
C(6)-H(6)	0.933(19)
C(7)-C(8)	1.388(2)
C(7)-H(7)	1.02(2)
C(8)-C(9)	1.384(2)
C(8)-H(8)	0.96(2)
C(9)-H(9)	0.968(18)
C(10)-C(20)	1.5272(18)
C(10)-C(11)	1.5473(18)
C(10)-H(10)	0.951(17)
C(11)-C(13)	1.527(2)
C(11)-C(12)	1.5329(19)
C(11)-H(11)	0.994(17)
C(12)-H(12A)	1.03(2)

C(12)-H(12B)	0.971(19)
C(12)-H(12C)	0.99(2)
C(13)-H(13A)	0.955(19)
C(13)-H(13B)	0.99(2)
C(13)-H(13C)	0.94(2)
C(14)-C(19)	1.385(2)
C(14)-C(15)	1.388(2)
C(15)-C(16)	1.390(2)
C(15)-H(15)	0.959(19)
C(16)-C(17)	1.384(2)
C(16)-H(16)	0.989(18)
C(17)-C(18)	1.385(2)
C(17)-H(17)	1.008(17)
C(18)-C(19)	1.396(2)
C(18)-H(18)	0.95(2)
C(19)-H(19)	0.935(19)
C(21)-H(21A)	0.959(18)
C(21)-H(21B)	0.98(2)
C(21)-H(21C)	0.95(2)

O(2)-S-O(1)	119.00(6)
O(2)-S-N(1)	109.07(6)
O(1)-S-N(1)	106.77(6)
O(2)-S-C(5)	106.94(6)
O(1)-S-C(5)	110.87(6)
N(1)-S-C(5)	103.04(6)
C(20)-O(4)-C(21)	115.58(12)
C(10)-N(1)-C(1)	121.15(11)
C(10)-N(1)-S	116.19(9)
C(1)-N(1)-S	118.08(9)
N(3)-N(2)-C(2)	109.04(11)
N(2)-N(3)-N(4)	107.30(11)
N(3)-N(4)-C(3)	110.81(10)
N(3)-N(4)-C(14)	119.65(11)
C(3)-N(4)-C(14)	128.59(11)
N(1)-C(1)-C(2)	115.02(11)
N(1)-C(1)-H(1A)	108.7(11)
C(2)-C(1)-H(1A)	107.8(10)

N(1)-C(1)-H(1B)	109.5(11)
C(2)-C(1)-H(1B)	108.2(10)
H(1A)-C(1)-H(1B)	107.5(14)
N(2)-C(2)-C(3)	108.85(12)
N(2)-C(2)-C(1)	119.57(12)
C(3)-C(2)-C(1)	131.46(13)
N(4)-C(3)-C(2)	103.99(11)
N(4)-C(3)-C(4)	123.41(11)
C(2)-C(3)-C(4)	132.58(12)
C(9)-C(4)-C(5)	117.87(13)
C(9)-C(4)-C(3)	120.97(12)
C(5)-C(4)-C(3)	121.15(12)
C(6)-C(5)-C(4)	121.57(13)
C(6)-C(5)-S	118.91(11)
C(4)-C(5)-S	119.13(10)
C(5)-C(6)-C(7)	119.66(14)
C(5)-C(6)-H(6)	118.8(11)
C(7)-C(6)-H(6)	121.6(11)
C(8)-C(7)-C(6)	119.63(13)
C(8)-C(7)-H(7)	120.9(11)
C(6)-C(7)-H(7)	119.4(11)
C(9)-C(8)-C(7)	120.61(13)
C(9)-C(8)-H(8)	117.8(11)
C(7)-C(8)-H(8)	121.6(11)
C(8)-C(9)-C(4)	120.61(13)
C(8)-C(9)-H(9)	120.3(9)
C(4)-C(9)-H(9)	119.1(9)
N(1)-C(10)-C(20)	111.06(11)
N(1)-C(10)-C(11)	110.66(10)
C(20)-C(10)-C(11)	112.73(11)
N(1)-C(10)-H(10)	105.1(9)
C(20)-C(10)-H(10)	106.8(9)
C(11)-C(10)-H(10)	110.2(9)
C(13)-C(11)-C(12)	110.39(13)
C(13)-C(11)-C(10)	109.18(11)
C(12)-C(11)-C(10)	110.75(11)
C(13)-C(11)-H(11)	110.1(9)
C(12)-C(11)-H(11)	109.2(9)

C(10)-C(11)-H(11)	107.3(9)
C(11)-C(12)-H(12A)	111.9(12)
C(11)-C(12)-H(12B)	108.8(11)
H(12A)-C(12)-H(12B)	108.0(16)
C(11)-C(12)-H(12C)	107.1(12)
H(12A)-C(12)-H(12C)	111.3(17)
H(12B)-C(12)-H(12C)	109.6(17)
C(11)-C(13)-H(13A)	112.4(11)
C(11)-C(13)-H(13B)	108.5(12)
H(13A)-C(13)-H(13B)	107.1(16)
C(11)-C(13)-H(13C)	109.1(13)
H(13A)-C(13)-H(13C)	109.1(16)
H(13B)-C(13)-H(13C)	110.6(18)
C(19)-C(14)-C(15)	121.22(13)
C(19)-C(14)-N(4)	119.69(13)
C(15)-C(14)-N(4)	119.08(12)
C(14)-C(15)-C(16)	119.42(14)
C(14)-C(15)-H(15)	119.8(11)
C(16)-C(15)-H(15)	120.6(11)
C(17)-C(16)-C(15)	120.09(15)
C(17)-C(16)-H(16)	120.7(10)
C(15)-C(16)-H(16)	119.2(10)
C(16)-C(17)-C(18)	119.98(13)
C(16)-C(17)-H(17)	118.5(10)
C(18)-C(17)-H(17)	121.4(10)
C(17)-C(18)-C(19)	120.67(14)
C(17)-C(18)-H(18)	121.0(11)
C(19)-C(18)-H(18)	118.3(11)
C(14)-C(19)-C(18)	118.60(15)
C(14)-C(19)-H(19)	117.9(10)
C(18)-C(19)-H(19)	123.5(11)
O(3)-C(20)-O(4)	124.13(13)
O(3)-C(20)-C(10)	124.85(13)
O(4)-C(20)-C(10)	111.02(12)
O(4)-C(21)-H(21A)	109.5(10)
O(4)-C(21)-H(21B)	113.0(12)
H(21A)-C(21)-H(21B)	109.4(16)
O(4)-C(21)-H(21C)	103.6(13)

H(21A)-C(21)-H(21C)	109.9(16)
H(21B)-C(21)-H(21C)	111.3(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C21H22N4O4S. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	14(1)	14(1)	14(1)	0(1)	0(1)	1(1)
O(1)	20(1)	17(1)	17(1)	2(1)	0(1)	2(1)
O(2)	16(1)	22(1)	19(1)	1(1)	0(1)	4(1)
O(3)	17(1)	27(1)	44(1)	14(1)	1(1)	1(1)
O(4)	19(1)	16(1)	29(1)	4(1)	-1(1)	-1(1)
N(1)	15(1)	16(1)	13(1)	0(1)	2(1)	-1(1)
N(2)	16(1)	20(1)	18(1)	0(1)	1(1)	-2(1)
N(3)	15(1)	21(1)	17(1)	0(1)	1(1)	-2(1)
N(4)	16(1)	17(1)	16(1)	0(1)	2(1)	2(1)
C(1)	16(1)	15(1)	16(1)	-1(1)	1(1)	-2(1)
C(2)	16(1)	15(1)	16(1)	2(1)	0(1)	0(1)
C(3)	15(1)	17(1)	14(1)	1(1)	0(1)	2(1)
C(4)	19(1)	18(1)	12(1)	-1(1)	1(1)	0(1)
C(5)	18(1)	17(1)	12(1)	0(1)	-2(1)	0(1)
C(6)	19(1)	24(1)	20(1)	-2(1)	0(1)	-3(1)
C(7)	26(1)	23(1)	26(1)	-4(1)	1(1)	-8(1)
C(8)	31(1)	16(1)	22(1)	-3(1)	2(1)	-4(1)
C(9)	23(1)	18(1)	16(1)	-2(1)	1(1)	1(1)
C(10)	15(1)	18(1)	14(1)	2(1)	1(1)	-2(1)
C(11)	18(1)	23(1)	15(1)	-1(1)	1(1)	-5(1)
C(12)	32(1)	34(1)	14(1)	0(1)	2(1)	-10(1)
C(13)	22(1)	26(1)	23(1)	-9(1)	0(1)	0(1)
C(14)	20(1)	16(1)	14(1)	1(1)	3(1)	1(1)
C(15)	20(1)	24(1)	20(1)	-1(1)	1(1)	4(1)
C(16)	27(1)	26(1)	19(1)	-1(1)	-1(1)	-1(1)
C(17)	30(1)	20(1)	18(1)	-2(1)	5(1)	-4(1)
C(18)	24(1)	17(1)	23(1)	-1(1)	9(1)	3(1)
C(19)	18(1)	18(1)	19(1)	2(1)	2(1)	1(1)
C(20)	18(1)	20(1)	15(1)	3(1)	-2(1)	-2(1)
C(21)	25(1)	16(1)	31(1)	4(1)	-2(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C21H22N4O4S.

	x	y	z	U(eq)
H(1A)	1205(17)	246(13)	1275(11)	15(4)
H(1B)	818(17)	1049(12)	641(13)	16(4)
H(6)	5331(18)	2727(13)	2101(13)	24(4)
H(7)	5190(20)	4391(15)	2394(15)	35(5)
H(8)	3044(18)	5016(14)	2656(13)	27(5)
H(9)	1250(17)	4026(11)	2729(11)	14(4)
H(10)	3975(16)	1808(11)	283(11)	7(3)
H(11)	2037(16)	817(11)	-740(11)	10(4)
H(12A)	2630(20)	2186(16)	-1676(15)	40(5)
H(12B)	3148(18)	1207(13)	-2145(13)	25(4)
H(12C)	4170(20)	1824(15)	-1553(15)	35(5)
H(13A)	3735(18)	-162(13)	-71(13)	24(4)
H(13B)	4760(20)	426(15)	-629(14)	34(5)
H(13C)	3730(20)	-216(15)	-1152(15)	37(5)
H(15)	2066(18)	2464(13)	4372(13)	26(5)
H(16)	2160(18)	3338(12)	5785(12)	18(4)
H(17)	295(16)	4143(12)	6341(12)	15(4)
H(18)	-1623(19)	4096(14)	5391(13)	26(5)
H(19)	-1641(18)	3245(12)	3961(12)	18(4)
H(21A)	2357(17)	4485(12)	381(13)	15(4)
H(21B)	1870(20)	4240(14)	-646(15)	36(5)
H(21C)	3300(20)	4619(16)	-464(15)	37(5)

Table 6. Torsion angles [°] for C21H22N4O4S.

O(2)-S-N(1)-C(10)	-45.45(11)
O(1)-S-N(1)-C(10)	-175.23(9)
C(5)-S-N(1)-C(10)	67.91(10)
O(2)-S-N(1)-C(1)	158.25(9)
O(1)-S-N(1)-C(1)	28.47(10)
C(5)-S-N(1)-C(1)	-88.39(10)
C(2)-N(2)-N(3)-N(4)	0.55(14)
N(2)-N(3)-N(4)-C(3)	-0.06(14)
N(2)-N(3)-N(4)-C(14)	-169.85(11)
C(10)-N(1)-C(1)-C(2)	-112.89(13)
S-N(1)-C(1)-C(2)	42.19(14)
N(3)-N(2)-C(2)-C(3)	-0.83(15)
N(3)-N(2)-C(2)-C(1)	175.55(11)
N(1)-C(1)-C(2)-N(2)	-164.34(11)
N(1)-C(1)-C(2)-C(3)	11.1(2)
N(3)-N(4)-C(3)-C(2)	-0.43(14)
C(14)-N(4)-C(3)-C(2)	168.20(12)
N(3)-N(4)-C(3)-C(4)	178.01(12)
C(14)-N(4)-C(3)-C(4)	-13.4(2)
N(2)-C(2)-C(3)-N(4)	0.75(14)
C(1)-C(2)-C(3)-N(4)	-175.05(13)
N(2)-C(2)-C(3)-C(4)	-177.48(13)
C(1)-C(2)-C(3)-C(4)	6.7(3)
N(4)-C(3)-C(4)-C(9)	-42.54(19)
C(2)-C(3)-C(4)-C(9)	135.41(16)
N(4)-C(3)-C(4)-C(5)	138.55(13)
C(2)-C(3)-C(4)-C(5)	-43.5(2)
C(9)-C(4)-C(5)-C(6)	1.80(19)
C(3)-C(4)-C(5)-C(6)	-179.26(12)
C(9)-C(4)-C(5)-S	-170.86(10)
C(3)-C(4)-C(5)-S	8.08(17)
O(2)-S-C(5)-C(6)	-0.88(12)
O(1)-S-C(5)-C(6)	130.29(11)
N(1)-S-C(5)-C(6)	-115.79(11)
O(2)-S-C(5)-C(4)	171.97(10)
O(1)-S-C(5)-C(4)	-56.85(12)

N(1)-S-C(5)-C(4)	57.06(11)
C(4)-C(5)-C(6)-C(7)	0.1(2)
S-C(5)-C(6)-C(7)	172.79(12)
C(5)-C(6)-C(7)-C(8)	-1.9(2)
C(6)-C(7)-C(8)-C(9)	1.7(2)
C(7)-C(8)-C(9)-C(4)	0.3(2)
C(5)-C(4)-C(9)-C(8)	-2.0(2)
C(3)-C(4)-C(9)-C(8)	179.08(12)
C(1)-N(1)-C(10)-C(20)	56.08(15)
S-N(1)-C(10)-C(20)	-99.45(12)
C(1)-N(1)-C(10)-C(11)	-69.92(15)
S-N(1)-C(10)-C(11)	134.56(10)
N(1)-C(10)-C(11)-C(13)	-64.27(15)
C(20)-C(10)-C(11)-C(13)	170.67(12)
N(1)-C(10)-C(11)-C(12)	173.98(12)
C(20)-C(10)-C(11)-C(12)	48.93(17)
N(3)-N(4)-C(14)-C(19)	-52.61(17)
C(3)-N(4)-C(14)-C(19)	139.63(14)
N(3)-N(4)-C(14)-C(15)	126.26(13)
C(3)-N(4)-C(14)-C(15)	-41.50(19)
C(19)-C(14)-C(15)-C(16)	-1.0(2)
N(4)-C(14)-C(15)-C(16)	-179.85(13)
C(14)-C(15)-C(16)-C(17)	1.6(2)
C(15)-C(16)-C(17)-C(18)	-0.8(2)
C(16)-C(17)-C(18)-C(19)	-0.7(2)
C(15)-C(14)-C(19)-C(18)	-0.4(2)
N(4)-C(14)-C(19)-C(18)	178.41(12)
C(17)-C(18)-C(19)-C(14)	1.3(2)
C(21)-O(4)-C(20)-O(3)	-1.4(2)
C(21)-O(4)-C(20)-C(10)	178.62(12)
N(1)-C(10)-C(20)-O(3)	-46.56(19)
C(11)-C(10)-C(20)-O(3)	78.28(18)
N(1)-C(10)-C(20)-O(4)	133.39(12)
C(11)-C(10)-C(20)-O(4)	-101.77(14)

Symmetry transformations used to generate equivalent atoms:

(*S*)-Methyl 2-(7,7-dioxido-1-phenyl-4,5-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*e*][1,2]thiazocin-6(1*H*)-yl)-3-methylbutanoate (4.89)

Table 1. Crystal data and structure refinement for C22H24N4O4S.

Empirical formula	C44 H48 N8 O8 S2	
Formula weight	881.02	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 15.0364(3) Å	α= 90°.
	b = 8.2478(2) Å	β= 94.0360(10)°.
	c = 17.7420(4) Å	γ = 90°.
Volume	2194.86(8) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	1.617 mm^{-1}	
F(000)	928	
Crystal size	0.16 x 0.07 x 0.05 mm^3	
Theta range for data collection	5.00 to 69.32°.	
Index ranges	-17<=h<=17, -8<=k<=9, -20<=l<=21	
Reflections collected	16054	
Independent reflections	3935 [R(int) = 0.0171]	
Completeness to theta = 66.00°	98.6 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.893	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3935 / 0 / 376	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0309, wR2 = 0.0822	
R indices (all data)	R1 = 0.0321, wR2 = 0.0832	
Largest diff. peak and hole	0.352 and -0.339 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C22H24N4O4S. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	2683(1)	3738(1)	965(1)	21(1)
O(1)	2237(1)	4886(1)	1414(1)	27(1)
O(2)	3006(1)	4244(1)	262(1)	29(1)
O(3)	3482(1)	-438(1)	930(1)	30(1)
O(4)	4504(1)	-340(1)	1910(1)	40(1)
N(1)	3539(1)	3058(1)	1494(1)	22(1)
N(2)	1620(1)	2974(1)	3246(1)	26(1)
N(3)	775(1)	3228(2)	3051(1)	27(1)
N(4)	625(1)	2705(1)	2329(1)	22(1)
C(1)	3564(1)	3154(2)	2326(1)	26(1)
C(2)	2989(1)	1913(2)	2714(1)	25(1)
C(3)	2016(1)	2296(2)	2656(1)	22(1)
C(4)	1388(1)	2122(2)	2061(1)	20(1)
C(5)	1426(1)	1425(2)	1300(1)	19(1)
C(6)	1961(1)	2071(1)	755(1)	19(1)
C(7)	1957(1)	1399(2)	36(1)	23(1)
C(8)	1439(1)	43(2)	-144(1)	26(1)
C(9)	925(1)	-630(2)	395(1)	26(1)
C(10)	907(1)	65(2)	1105(1)	23(1)
C(11)	4205(1)	2056(2)	1133(1)	24(1)
C(12)	5168(1)	2653(2)	1284(1)	33(1)
C(13)	5748(1)	1693(3)	767(1)	53(1)
C(14)	5233(1)	4470(2)	1144(1)	41(1)
C(15)	-225(1)	3021(2)	1932(1)	23(1)
C(16)	-253(1)	4007(2)	1299(1)	28(1)
C(17)	-1074(1)	4376(2)	931(1)	33(1)
C(18)	-1851(1)	3767(2)	1200(1)	32(1)
C(19)	-1810(1)	2783(2)	1833(1)	32(1)
C(20)	-993(1)	2394(2)	2207(1)	27(1)
C(21)	4104(1)	291(2)	1377(1)	25(1)
C(22)	3230(1)	-2065(2)	1141(1)	39(1)

Table 3. Bond lengths [Å] and angles [°] for C22H24N4O4S.

S-O(2)	1.4328(9)
S-O(1)	1.4330(10)
S-N(1)	1.6378(10)
S-C(6)	1.7748(12)
O(3)-C(21)	1.3265(16)
O(3)-C(22)	1.4506(17)
O(4)-C(21)	1.2029(16)
N(1)-C(1)	1.4758(16)
N(1)-C(11)	1.4790(16)
N(2)-N(3)	1.3102(16)
N(2)-C(3)	1.3610(16)
N(3)-N(4)	1.3552(15)
N(4)-C(4)	1.3596(16)
N(4)-C(15)	1.4396(16)
C(1)-C(2)	1.5341(19)
C(1)-H(1A)	0.982(16)
C(1)-H(1B)	0.980(17)
C(2)-C(3)	1.4930(17)
C(2)-H(2A)	0.968(16)
C(2)-H(2B)	0.975(17)
C(3)-C(4)	1.3730(18)
C(4)-C(5)	1.4736(16)
C(5)-C(10)	1.3960(18)
C(5)-C(6)	1.4047(17)
C(6)-C(7)	1.3902(17)
C(7)-C(8)	1.3878(19)
C(7)-H(7)	0.930(16)
C(8)-C(9)	1.3864(19)
C(8)-H(8)	0.967(16)
C(9)-C(10)	1.3861(18)
C(9)-H(9)	0.971(18)
C(10)-H(10)	0.958(15)
C(11)-C(21)	1.5287(19)
C(11)-C(12)	1.5348(17)
C(11)-H(11)	0.977(14)
C(12)-C(14)	1.523(2)

C(12)-C(13)	1.531(2)
C(12)-H(12)	1.004(18)
C(13)-H(13A)	0.98(2)
C(13)-H(13B)	0.96(2)
C(13)-H(13C)	0.99(2)
C(14)-H(14A)	0.981(18)
C(14)-H(14B)	0.99(2)
C(14)-H(14C)	0.96(2)
C(15)-C(20)	1.3850(19)
C(15)-C(16)	1.3854(19)
C(16)-C(17)	1.390(2)
C(16)-H(16)	0.957(18)
C(17)-C(18)	1.387(2)
C(17)-H(17)	0.969(19)
C(18)-C(19)	1.383(2)
C(18)-H(18)	0.977(18)
C(19)-C(20)	1.392(2)
C(19)-H(19)	0.969(18)
C(20)-H(20)	0.951(17)
C(22)-H(22A)	0.97(2)
C(22)-H(22B)	0.94(2)
C(22)-H(22C)	1.00(2)

O(2)-S-O(1)	119.46(6)
O(2)-S-N(1)	107.32(5)
O(1)-S-N(1)	106.67(5)
O(2)-S-C(6)	106.41(6)
O(1)-S-C(6)	109.00(6)
N(1)-S-C(6)	107.45(5)
C(21)-O(3)-C(22)	116.85(12)
C(1)-N(1)-C(11)	119.49(10)
C(1)-N(1)-S	121.25(9)
C(11)-N(1)-S	118.16(8)
N(3)-N(2)-C(3)	109.32(10)
N(2)-N(3)-N(4)	107.03(10)
N(3)-N(4)-C(4)	110.75(10)
N(3)-N(4)-C(15)	119.16(10)
C(4)-N(4)-C(15)	129.46(10)

N(1)-C(1)-C(2)	115.96(10)
N(1)-C(1)-H(1A)	105.2(9)
C(2)-C(1)-H(1A)	109.8(10)
N(1)-C(1)-H(1B)	108.7(9)
C(2)-C(1)-H(1B)	108.6(9)
H(1A)-C(1)-H(1B)	108.3(13)
C(3)-C(2)-C(1)	114.06(11)
C(3)-C(2)-H(2A)	106.9(9)
C(1)-C(2)-H(2A)	107.4(9)
C(3)-C(2)-H(2B)	111.2(9)
C(1)-C(2)-H(2B)	109.4(9)
H(2A)-C(2)-H(2B)	107.6(13)
N(2)-C(3)-C(4)	108.62(11)
N(2)-C(3)-C(2)	120.89(11)
C(4)-C(3)-C(2)	130.46(11)
N(4)-C(4)-C(3)	104.28(10)
N(4)-C(4)-C(5)	123.12(11)
C(3)-C(4)-C(5)	132.55(11)
C(10)-C(5)-C(6)	118.13(11)
C(10)-C(5)-C(4)	118.91(11)
C(6)-C(5)-C(4)	122.96(11)
C(7)-C(6)-C(5)	120.95(11)
C(7)-C(6)-S	117.67(9)
C(5)-C(6)-S	121.36(9)
C(8)-C(7)-C(6)	119.89(12)
C(8)-C(7)-H(7)	119.3(10)
C(6)-C(7)-H(7)	120.8(10)
C(9)-C(8)-C(7)	119.69(12)
C(9)-C(8)-H(8)	118.7(9)
C(7)-C(8)-H(8)	121.6(9)
C(10)-C(9)-C(8)	120.54(12)
C(10)-C(9)-H(9)	118.8(10)
C(8)-C(9)-H(9)	120.6(10)
C(9)-C(10)-C(5)	120.74(11)
C(9)-C(10)-H(10)	121.0(9)
C(5)-C(10)-H(10)	118.2(9)
N(1)-C(11)-C(21)	109.05(10)
N(1)-C(11)-C(12)	113.81(11)

C(21)-C(11)-C(12)	111.54(11)
N(1)-C(11)-H(11)	106.4(8)
C(21)-C(11)-H(11)	107.2(8)
C(12)-C(11)-H(11)	108.5(8)
C(14)-C(12)-C(13)	111.40(15)
C(14)-C(12)-C(11)	110.99(13)
C(13)-C(12)-C(11)	107.43(12)
C(14)-C(12)-H(12)	109.6(11)
C(13)-C(12)-H(12)	111.1(10)
C(11)-C(12)-H(12)	106.2(10)
C(12)-C(13)-H(13A)	110.6(13)
C(12)-C(13)-H(13B)	110.5(12)
H(13A)-C(13)-H(13B)	105.7(18)
C(12)-C(13)-H(13C)	110.4(13)
H(13A)-C(13)-H(13C)	108.8(18)
H(13B)-C(13)-H(13C)	110.7(18)
C(12)-C(14)-H(14A)	110.9(11)
C(12)-C(14)-H(14B)	112.9(13)
H(14A)-C(14)-H(14B)	107.2(16)
C(12)-C(14)-H(14C)	107.8(14)
H(14A)-C(14)-H(14C)	110.0(16)
H(14B)-C(14)-H(14C)	108.0(17)
C(20)-C(15)-C(16)	121.75(12)
C(20)-C(15)-N(4)	119.65(12)
C(16)-C(15)-N(4)	118.55(11)
C(15)-C(16)-C(17)	118.98(13)
C(15)-C(16)-H(16)	122.1(10)
C(17)-C(16)-H(16)	118.9(10)
C(18)-C(17)-C(16)	120.08(14)
C(18)-C(17)-H(17)	120.2(10)
C(16)-C(17)-H(17)	119.7(10)
C(19)-C(18)-C(17)	120.10(13)
C(19)-C(18)-H(18)	119.6(10)
C(17)-C(18)-H(18)	120.3(10)
C(18)-C(19)-C(20)	120.64(13)
C(18)-C(19)-H(19)	120.3(11)
C(20)-C(19)-H(19)	119.0(11)
C(15)-C(20)-C(19)	118.44(13)

C(15)-C(20)-H(20)	119.7(9)
C(19)-C(20)-H(20)	121.9(9)
O(4)-C(21)-O(3)	124.47(13)
O(4)-C(21)-C(11)	125.47(12)
O(3)-C(21)-C(11)	110.01(10)
O(3)-C(22)-H(22A)	110.6(12)
O(3)-C(22)-H(22B)	109.9(15)
H(22A)-C(22)-H(22B)	112.1(18)
O(3)-C(22)-H(22C)	102.9(14)
H(22A)-C(22)-H(22C)	107.5(18)
H(22B)-C(22)-H(22C)	113.5(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C22H24N4O4S. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	23(1)	17(1)	24(1)	3(1)	1(1)	-3(1)
O(1)	29(1)	18(1)	34(1)	0(1)	1(1)	0(1)
O(2)	30(1)	26(1)	30(1)	8(1)	2(1)	-5(1)
O(3)	32(1)	18(1)	38(1)	2(1)	-4(1)	-3(1)
O(4)	45(1)	36(1)	38(1)	2(1)	-10(1)	12(1)
N(1)	21(1)	21(1)	24(1)	-2(1)	0(1)	-2(1)
N(2)	28(1)	30(1)	21(1)	-2(1)	2(1)	5(1)
N(3)	28(1)	31(1)	21(1)	-4(1)	3(1)	6(1)
N(4)	23(1)	23(1)	21(1)	-1(1)	3(1)	3(1)
C(1)	24(1)	28(1)	25(1)	-5(1)	-2(1)	0(1)
C(2)	25(1)	29(1)	21(1)	0(1)	0(1)	6(1)
C(3)	25(1)	21(1)	19(1)	1(1)	2(1)	3(1)
C(4)	22(1)	17(1)	22(1)	2(1)	4(1)	2(1)
C(5)	19(1)	18(1)	19(1)	1(1)	0(1)	3(1)
C(6)	18(1)	18(1)	21(1)	1(1)	-1(1)	0(1)
C(7)	23(1)	27(1)	20(1)	2(1)	2(1)	1(1)
C(8)	28(1)	28(1)	21(1)	-5(1)	-1(1)	1(1)
C(9)	26(1)	22(1)	29(1)	-3(1)	-3(1)	-4(1)
C(10)	21(1)	22(1)	25(1)	2(1)	2(1)	-1(1)
C(11)	22(1)	25(1)	25(1)	-4(1)	2(1)	-2(1)
C(12)	22(1)	42(1)	37(1)	-11(1)	3(1)	-6(1)
C(13)	26(1)	67(1)	67(1)	-29(1)	15(1)	-10(1)
C(14)	34(1)	46(1)	42(1)	-8(1)	6(1)	-21(1)
C(15)	23(1)	22(1)	25(1)	-5(1)	2(1)	5(1)
C(16)	26(1)	26(1)	32(1)	1(1)	2(1)	3(1)
C(17)	34(1)	28(1)	35(1)	1(1)	-3(1)	7(1)
C(18)	25(1)	32(1)	39(1)	-8(1)	-5(1)	6(1)
C(19)	24(1)	34(1)	39(1)	-11(1)	5(1)	-2(1)
C(20)	28(1)	26(1)	28(1)	-5(1)	5(1)	1(1)
C(21)	22(1)	27(1)	25(1)	-3(1)	3(1)	5(1)
C(22)	43(1)	19(1)	56(1)	5(1)	5(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C22H24N4O4S.

	x	y	z	U(eq)
H(1A)	4194(11)	3010(20)	2499(9)	29(4)
H(1B)	3382(10)	4250(20)	2469(8)	26(4)
H(2A)	3182(10)	1910(20)	3246(9)	28(4)
H(2B)	3101(10)	830(20)	2517(9)	27(4)
H(7)	2281(10)	1870(20)	-333(9)	26(4)
H(8)	1419(10)	-440(20)	-641(9)	27(4)
H(9)	569(11)	-1590(20)	281(9)	34(4)
H(10)	539(10)	-373(19)	1475(8)	23(4)
H(11)	4049(9)	2103(17)	590(8)	15(3)
H(12)	5337(11)	2420(20)	1831(10)	39(4)
H(13A)	6376(15)	1980(30)	867(12)	63(6)
H(13B)	5709(14)	550(30)	869(11)	53(6)
H(13C)	5570(14)	1920(30)	232(13)	58(6)
H(14A)	4961(11)	5090(20)	1541(10)	38(4)
H(14B)	4930(14)	4810(30)	654(12)	53(5)
H(14C)	5850(15)	4740(30)	1137(12)	60(6)
H(16)	275(12)	4460(20)	1114(9)	34(4)
H(17)	-1101(12)	5060(20)	486(10)	40(5)
H(18)	-2429(12)	4000(20)	936(10)	39(5)
H(19)	-2352(12)	2360(20)	2023(10)	42(5)
H(20)	-952(10)	1720(20)	2641(9)	29(4)
H(22A)	3741(13)	-2780(30)	1155(11)	48(5)
H(22B)	2964(15)	-2040(30)	1604(13)	66(6)
H(22C)	2813(15)	-2410(30)	706(13)	69(7)

Table 6. Torsion angles [°] for C22H24N4O4S.

O(2)-S-N(1)-C(1)	151.12(10)
O(1)-S-N(1)-C(1)	21.99(11)
C(6)-S-N(1)-C(1)	-94.78(10)
O(2)-S-N(1)-C(11)	-40.88(10)
O(1)-S-N(1)-C(11)	-170.01(9)
C(6)-S-N(1)-C(11)	73.22(10)
C(3)-N(2)-N(3)-N(4)	0.17(15)
N(2)-N(3)-N(4)-C(4)	-0.46(15)
N(2)-N(3)-N(4)-C(15)	-172.23(11)
C(11)-N(1)-C(1)-C(2)	-91.88(13)
S-N(1)-C(1)-C(2)	75.96(13)
N(1)-C(1)-C(2)-C(3)	-76.43(14)
N(3)-N(2)-C(3)-C(4)	0.18(15)
N(3)-N(2)-C(3)-C(2)	178.49(12)
C(1)-C(2)-C(3)-N(2)	-101.28(14)
C(1)-C(2)-C(3)-C(4)	76.62(18)
N(3)-N(4)-C(4)-C(3)	0.55(14)
C(15)-N(4)-C(4)-C(3)	171.23(12)
N(3)-N(4)-C(4)-C(5)	178.17(11)
C(15)-N(4)-C(4)-C(5)	-11.1(2)
N(2)-C(3)-C(4)-N(4)	-0.44(14)
C(2)-C(3)-C(4)-N(4)	-178.53(13)
N(2)-C(3)-C(4)-C(5)	-177.73(13)
C(2)-C(3)-C(4)-C(5)	4.2(2)
N(4)-C(4)-C(5)-C(10)	-60.21(16)
C(3)-C(4)-C(5)-C(10)	116.66(16)
N(4)-C(4)-C(5)-C(6)	119.56(14)
C(3)-C(4)-C(5)-C(6)	-63.58(19)
C(10)-C(5)-C(6)-C(7)	1.51(17)
C(4)-C(5)-C(6)-C(7)	-178.26(11)
C(10)-C(5)-C(6)-S	-176.94(9)
C(4)-C(5)-C(6)-S	3.30(16)
O(2)-S-C(6)-C(7)	10.86(11)
O(1)-S-C(6)-C(7)	140.93(10)
N(1)-S-C(6)-C(7)	-103.84(10)
O(2)-S-C(6)-C(5)	-170.64(10)

O(1)-S-C(6)-C(5)	-40.57(11)
N(1)-S-C(6)-C(5)	74.66(11)
C(5)-C(6)-C(7)-C(8)	-1.79(18)
S-C(6)-C(7)-C(8)	176.71(10)
C(6)-C(7)-C(8)-C(9)	0.20(19)
C(7)-C(8)-C(9)-C(10)	1.6(2)
C(8)-C(9)-C(10)-C(5)	-1.92(19)
C(6)-C(5)-C(10)-C(9)	0.34(18)
C(4)-C(5)-C(10)-C(9)	-179.88(11)
C(1)-N(1)-C(11)-C(21)	61.16(14)
S-N(1)-C(11)-C(21)	-107.05(10)
C(1)-N(1)-C(11)-C(12)	-64.07(15)
S-N(1)-C(11)-C(12)	127.72(11)
N(1)-C(11)-C(12)-C(14)	-48.10(16)
C(21)-C(11)-C(12)-C(14)	-171.99(12)
N(1)-C(11)-C(12)-C(13)	-170.11(14)
C(21)-C(11)-C(12)-C(13)	66.00(17)
N(3)-N(4)-C(15)-C(20)	-61.07(16)
C(4)-N(4)-C(15)-C(20)	128.91(14)
N(3)-N(4)-C(15)-C(16)	116.34(13)
C(4)-N(4)-C(15)-C(16)	-53.68(19)
C(20)-C(15)-C(16)-C(17)	0.1(2)
N(4)-C(15)-C(16)-C(17)	-177.30(12)
C(15)-C(16)-C(17)-C(18)	0.3(2)
C(16)-C(17)-C(18)-C(19)	-0.4(2)
C(17)-C(18)-C(19)-C(20)	0.0(2)
C(16)-C(15)-C(20)-C(19)	-0.4(2)
N(4)-C(15)-C(20)-C(19)	176.95(12)
C(18)-C(19)-C(20)-C(15)	0.3(2)
C(22)-O(3)-C(21)-O(4)	4.78(19)
C(22)-O(3)-C(21)-C(11)	-172.89(12)
N(1)-C(11)-C(21)-O(4)	-92.14(15)
C(12)-C(11)-C(21)-O(4)	34.39(18)
N(1)-C(11)-C(21)-O(3)	85.50(12)
C(12)-C(11)-C(21)-O(3)	-147.97(11)

Symmetry transformations used to generate equivalent atoms: